CONTENTS

The American Journal of Medicine

VOL. IV JUNE, 1948 No. 6

Editorial

Pain and Dystrophy in the Extremities . . . . . ROY H. TURNER 789

Clinical Studies

Dynamics of the Left Auricle in Mitral Valve Lesions. Fluorocardiographic Study
ALDO A. LUISADA and FELIX G. FLEISCHNER 791

Fluorocardiographic tracings represent a refinement of technic which, as this study makes clear, will throw new light upon the dynamics of the normal and abnormal heart. The evidence presented argues against the occurrence of mitral stenosis unaccompanied by mitral insufficiency.

Application of Microplethysmography to the Diagnosis of Patent Ductus Arteriosus and Coarctation of the Aorta RAYMOND S. MEGIBOW and SERGEI FEITELBERG 798

Microplethysmography is found to afford useful complementary information in the diagnosis of patent ductus and coarctation of the aorta.

Pheochromocytoma. Report of a Case, with a New Diagnostic Test
VICTOR GUARNERI and JAMES A. EVANS 806

A classic case of pheochromocytoma, successfully operated upon, with histologic confirmation of the diagnosis. Mecholyl unexpectedly was found to cause marked hypertension in this patient apparently by direct stimulation of the chromaffin tissue of the tumor. A test for pheochromocytoma, based on this observation, is described.

Absorption and Metabolism of Lipiodol after Oral Administration. Method for the Study of Fat Absorption and Fat Metabolism in Man . . . . J. GROEN 814

A study of the absorption and metabolism of fat by means of lipiodol administered orally. The fate of the lipiodol was followed by serial x-ray films of the gastrointestinal tract and by urinary and fecal iodine determinations. Delayed and decreased fat absorption could be demonstrated in sprue and other diseases.

Reiter's Syndrome. A Report on Four Patients Treated with Streptomycin
THOMAS A. WARTHIN 827

A report of four cases of Reiter's syndrome of unusual interest because of the recovery of pleuropneumonia-like organisms, the appearance of myocardial changes and the apparent response to streptomycin.

Contents continued on page 5

for the first time
in pharmaceutical history—

vi-syneral
injectable

1. Ready to inject—no mixing, no diluting, no heating.
2. Free from local irritation, characteristic of parenteral oil solutions.

*special process developed in U. S. Vitamin Corporation research laboratories and protected by U. S. Patent No. 2,417,299.

Detailed literature and sample

u. s. vitamin corporation
casimir funk laboratories, inc. (affiliate)
250 E 43rd Street • New York 17, N. Y.

CONTENTS

The American Journal of Medicine

VOL. IV JUNE, 1948 No. 6

Contents continued from page 3

Clinical Value of Examination of the Gastric Contents for Tubercle Bacilli
ANDREW L. BANYAI 836

An enthusiastic appraisal of the value of bacteriologic examination of the fasting gastric contents in pulmonary and extrapulmonary forms of tuberculosis. Detailed, practical information regarding technics and indications is given.

Technical Aspects of Therapeutic Malaria
LAWRENCE I. KAPLAN and HILTON S. READ 846

The authors make specific recommendations in the technic of inducing and regulating malaria in the treatment of neurosyphilis. Stressed are the advantages of quantitative parasite counts and the use of heterologous strains of P. vivax for reinoculation of subjects who exhibit partially immune reactions following the original infection with the standard strain.

Left Vocal Cord Paralysis Associated with Cardiac Disease
DAVID A. DOLOWITZ and C. S. LEWIS 856

Paralysis of the left recurrent nerve occurs in association with heart disease frequently enough to indicate some causal relationship. The authors discuss this association and add two illustrative cases and cite anatomic studies.

Parenteral Benadryl in Allergy SIDNEY FRIEDLAENDER and ALEX S. FRIEDLAENDER 863

An exploratory examination of the possible therapeutic value of parenteral administration of benadryl.

Review

Rickettsialpox in New York City . . . . . MORRIS GREENBERG 866

Dr. Greenberg gives a concise, authoritative summary of the available knowledge of rickettsialpox, a newly discovered rickettsial disease of considerable clinical interest.

Seminars on Hypertension

Consideration of Human Hypertension with Respect to Its Renal Origin and Therapy
WILLIAM GOLDRING 875

Dr. Goldring was asked to summarize and appraise the preceding seminars on hypertension. He has limited himself to the problem of the possible renal origin of hypertension, and to methods of treatment. His discussion is critical, forthright and disillusioning.

Contents continued on page 7

in the management of simple diarrheas

"TOMECTIN"

"TOMECTIN" *is a combination of nickel pectinate and dried fresh tomato pulp, two therapeutic agents which have been found of value in the management of diarrheas of non-specific origin.*

The detoxifying[1,2] *and bacteriostatic*[3] *properties of nickel pectinate as well as its antihemorrhagic effect*[4] *have proved of clinical assistance*[5] *in the treatment of various diarrheal conditions including bacillary dysentery. Morrison reports*[6] *that with dried tomato pulp, diarrhea from simple or non-organic cause was usually arrested within 24 hours following treatment. Nickel pectinate and dried tomato pulp have been found, in many instances, to bring about a favorable response when other antidiarrheal medication had failed.*[5,6]

"Tomectin" will appeal to infants, children and adults because, dispersed in water, it forms a preparation having the refreshing tartness of tomato juice. From the standpoint of therapeutic effectiveness, simplicity of administration and palatability, "Tomectin" will prove a valuable antidiarrheal medication.

"Tomectin," No. 951, is presented in wide-mouthed bottles each containing 50 grams. Each gram contains:

Nickel pectinate	*150.0 mg.*
Sodium chloride	*50.0 mg.*
Together with all factors naturally present in dried fresh tomato pulp	*800.0 mg.*

[1] Malyoth, G.: Klin. Wchnschr. *13*:51, 1934.
[2] Bittner, J. E., Jr.: Northwest Med. *35*:445 (Dec.) 1936.
[3] Myers, P. B., and Rouse, A. H.: Am. J. Digest. Dis. *7*:39 (Jan.) 1940.
[4] Powers, J. L.: Bull. National Formulary Committee *9*:5 (Oct.) 1940.
[5] Block, L. H., Tarnowski, A., and Green, B. L.: Am. J. Digest. Dis. *6*:96 (Apr.) 1939.
[6] Morrison, L. M.: Am. J. Digest. Dis. *13*:196 (June) 1946.

"TOMECTIN"

Nickel Pectinate Compound

Ayerst

Ayerst, McKenna & Harrison Limited

22 East 40th Street, New York 16, N. Y.

4850

CONTENTS

The American Journal of Medicine

VOL. IV JUNE, 1948 No. 6

Contents continued from page 5

Combined Staff Clinics

Congenital Heart Disease 886

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—A lucid presentation of the use of catheterization technics to obtain a more precise diagnosis in congenital anomalies of the heart and great vessels, to define indications for surgery and to evaluate the results of operative interference. Representative cases are cited and discussed.

Clinico-pathologic Conference

Convulsions and Hepatic Disease 902

Clinico-pathologic Conference (Washington University School of Medicine)—This conference deals informatively with a particularly interesting aspect of liver disease, the mechanisms of which are still obscure.

Case Reports

Gout in a Negro Family . . . . . ABRAHAM COHEN 911

Tophaceous gout occurring in three negro brothers.

Long-standing Case of Widespread Tuberculosis and Acute Colon Bacillus Infection Treated by Streptomycin. . . . . WM. EGBERT ROBERTSON 916

An interesting account of the effect of streptomycin in a patient with tuberculosis and intercurrent infections due to E. coli, with general comments on streptomycin therapy.

Marked Insulin Resistance in Diabetes Mellitus

MAXWELL G. BERRY and FERDINAND C. HELWIG 923

An interesting case of insulin resistant diabetes mellitus, with necropsy disclosing acute pancreatitis.

Phosphorus Poisoning with Recovery Accompanied by Electrocardiographic Changes

ROBERT A. NEWBURGER, SAMUEL B. BEASER and HARRY SHWACHMAN 927

Reversible changes in the hemopoietic system, heart and liver following mild phosphorus poisoning are described.

Author Index to Volume IV 931

Subject Index to Volume IV 932

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Material published in THE AMERICAN JOURNAL OF MEDICINE is copyrighted and may not be reproduced without permission of the publishers.

Change of address must reach us by the 15th of the month preceding month of issue.

PREPARATION OF MANUSCRIPTS

Text. Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

Illustrations. Illustrations must be in the form of glossy prints or drawings in black ink (*never* in blue). On the back of each illustration the figure number, author's name and an indication of the top of the picture should be given. Legends for illustrations are to be typewritten in a single list, with numbers corresponding to those on the photographs and drawings. Please do not attach legends to the pictures themselves.

Bibliographies. Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

The subscription price of THE AMERICAN JOURNAL OF MEDICINE, is $10.00 per year in advance in the United States; $12.00 in Canada and Pan-American countries and $15.00 in foreign countries. Current single numbers $2.00. All Special Numbers $4.00. Prices for such back numbers as are available will be quoted on request.

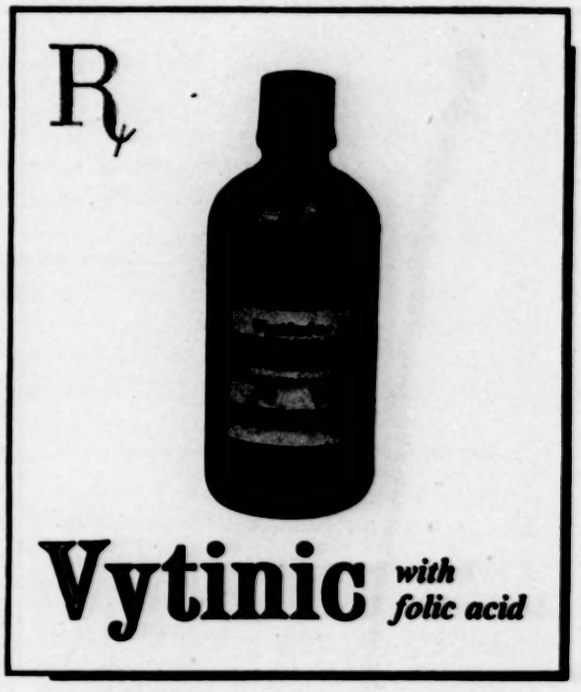
Address all correspondence to

The American Journal of Medicine · 49 West 45th Street · New York 19

designed for both

the physician's approval . . .

the patient's acceptance . . .



Vytinic, Bristol's new hematinic with folic acid, will win both the physician's approval and the patient's cooperation.

Its formula reflects the modern approach to comprehensive treatment of secondary anemia from rapid hemoglobin restoration to oxygen utilization in the cell. It aims to replace essential factors certainly deficient in hemorrhagic anemia and frequently deficient in that of nutritional origin.

Vytinic will win your patients' cooperation because it is a readily tolerated liquid of agreeable taste and appearance—easy to take over long periods. It will have especial appeal in pediatrics and geriatrics.

Each fluidounce contains:

Ferric Ammonium Citrate, USP	390 mg.
Thiamin Hydrochloride (Vitamin B_1)	10 mg.
Riboflavin (Vitamin B_2)	4 mg.
Niacinamide	100 mg.
Liver extract derived from 20 Gm. of fresh liver	
Folic Acid	2 mg.

Available in bottles of 12 oz. and 1 gal.
Send for tasting sample

***Dosage:** For adults—one tablespoonful, t.i.d., during, or immediately after meals.*
Children—in proportion to their age.
The suggested daily adult dose provides the following multiples of the minimum daily requirement for adults: iron—10, vitamin B_1—15, vitamin B_2—3, plus adequate amounts of niacinamide, liver extract and folic acid.

Use the *safest* antihistaminic *first*... Neohetramine

"Clinically, Neohetramine has an advantage over all other antihistaminics investigated, in that it is extremely well tolerated, and may often be used successfully in patients who are unable to take other drugs of this series because of unpleasant side actions."

Friedlaender, S., and A. S. Friedlaender, American College of Physicians, Milwaukee, 15 Nov. 1947.

Neohetramine is by far the safest antihistaminic. It maintains a high average of effectiveness and causes the fewest side reactions. Only 1 per cent of 1000 patients had to discontinue treatment.

Trial-and-error is the watchword in prescribing antiallergic drugs. Idiosyncrasies of the patient make it difficult to foresee which antihistaminic will afford the greatest symptomatic relief—or cause the lowest incidence of side effects. Therefore—try the *safest* antihistaminic *first*.

***Dosage:* 50 to 100 mg. three or four times a day, preferably after meals and at bedtime.**

Neohetramine

TRADEMARK

BRAND OF THONZYLAMINE HYDROCHLORIDE

N, N-dimethyl-N'-p-methoxybenzyl-N'-(2-pyrimidyl) ethylenediamine monohydrochloride, made by Nepera Chemical Co., Inc.

25, 50, and 100 mg. tablets, bottles of 100 and 1000.

DISTRIBUTED BY

WYETH INCORPORATED • PHILADELPHIA 3, PA.

Wyeth ®

IN PEPTIC ULCER... DRAMATICALLY EFFECTIVE

AVAILABLE: Resinat Capsules (0.25 Gm.), bottles of 50, 100, 500 and 1,000. Resinat Powder (1 Gm. packets), in boxes of 50 and 100.

Literature and samples available upon request.

[redacted]

An insoluble, non-absorbable anion exchange resin. Chemically inert, yet therapeutically effective in the management of peptic ulcer.

SUPERIOR ACTION:

1. Normalizes Gastric Acidity by Adsorption Without "Rebound"
2. Inactivates Pepsin

OUTSTANDING ADVANTAGES:

1. Does Not Cause Diarrhea or Constipation
2. Does Not Alter the Acid-Base Balance. Cannot Produce Alkalosis
3. Does Not Remove Phosphate or Chloride Ions
4. Innocuous, Even in Large Doses for Prolonged Periods

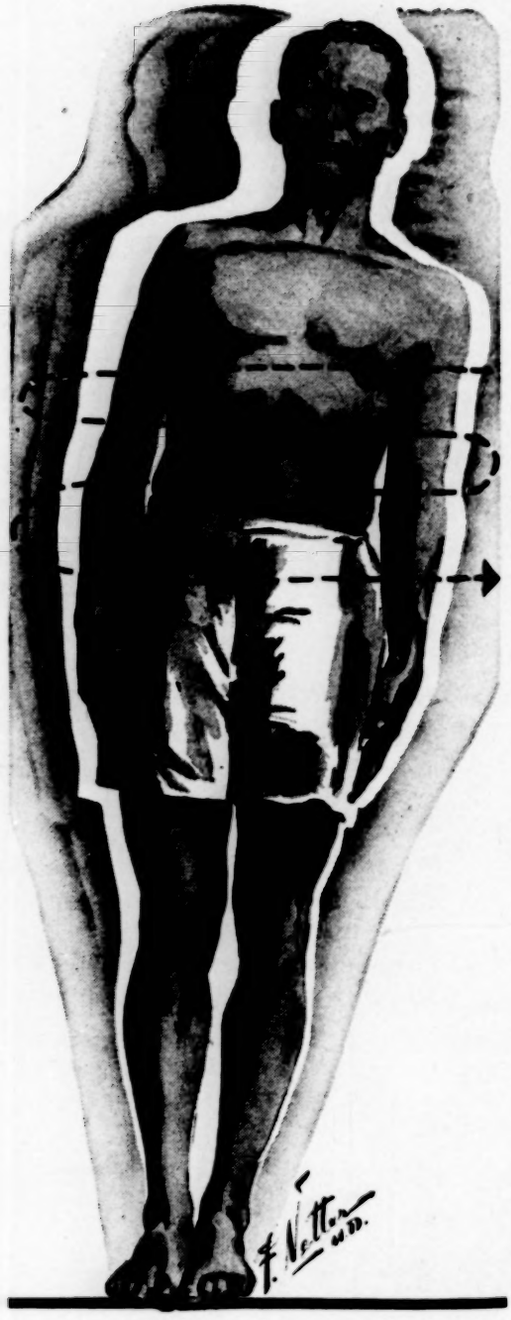
Dosage: Two or more capsules, or contents of one glassine packet, taken in water or milk, every two hours or as required.

RESINAT

Capsules and Powder (on prescription only)

THE NATIONAL DRUG COMPANY • PHILADELPHIA 44, PENNSYLVANIA

Pharmaceuticals • Biologicals • Biochemicals for the Medical Profession



POSITIVE ROMBERG

A positive Romberg test (Brauch-Romberg symptom) is one of the more characteristic evidences of cord involvement in pernicious anemia. Because of impaired position sense, the patient sways from side to side when he stands with feet together and eyes closed.

Early, adequate and persistent therapy is essential for the prevention or control of spinal cord affection in pernicious anemia. This is most important since neural involvement may cripple or incapacitate the patient. The *quality* of the liver preparation employed thus becomes of utmost significance. In the production of ARMOUR LIVER PREPARATIONS every precaution is taken to assure therapeutic efficacy. The ARMOUR LABORATORIES has available the world's largest supply of fresh raw animal material. Skill and care are exercised to preserve the active blood regenerating constituents of the fresh liver—the hemopoietic principle as well as secondary factors. The finished products are tested for potency on actual pernicious anemia patients in relapse.

Have confidence in the preparation you prescribe—specify "ARMOUR"

ARMOUR *Liver Preparations*

Liver Liquid Parenteral
4 U. S. P. Injectable Units per cc. 1 cc., 5 cc., and 10 cc. rubber-capped vials. A preparation retaining the secondary hemopoietic factors and most of the vitamin content of the liver.

10 U. S. P. Injectable Units per cc. 1 cc., 5cc. and 10 cc. rubber-capped vials.

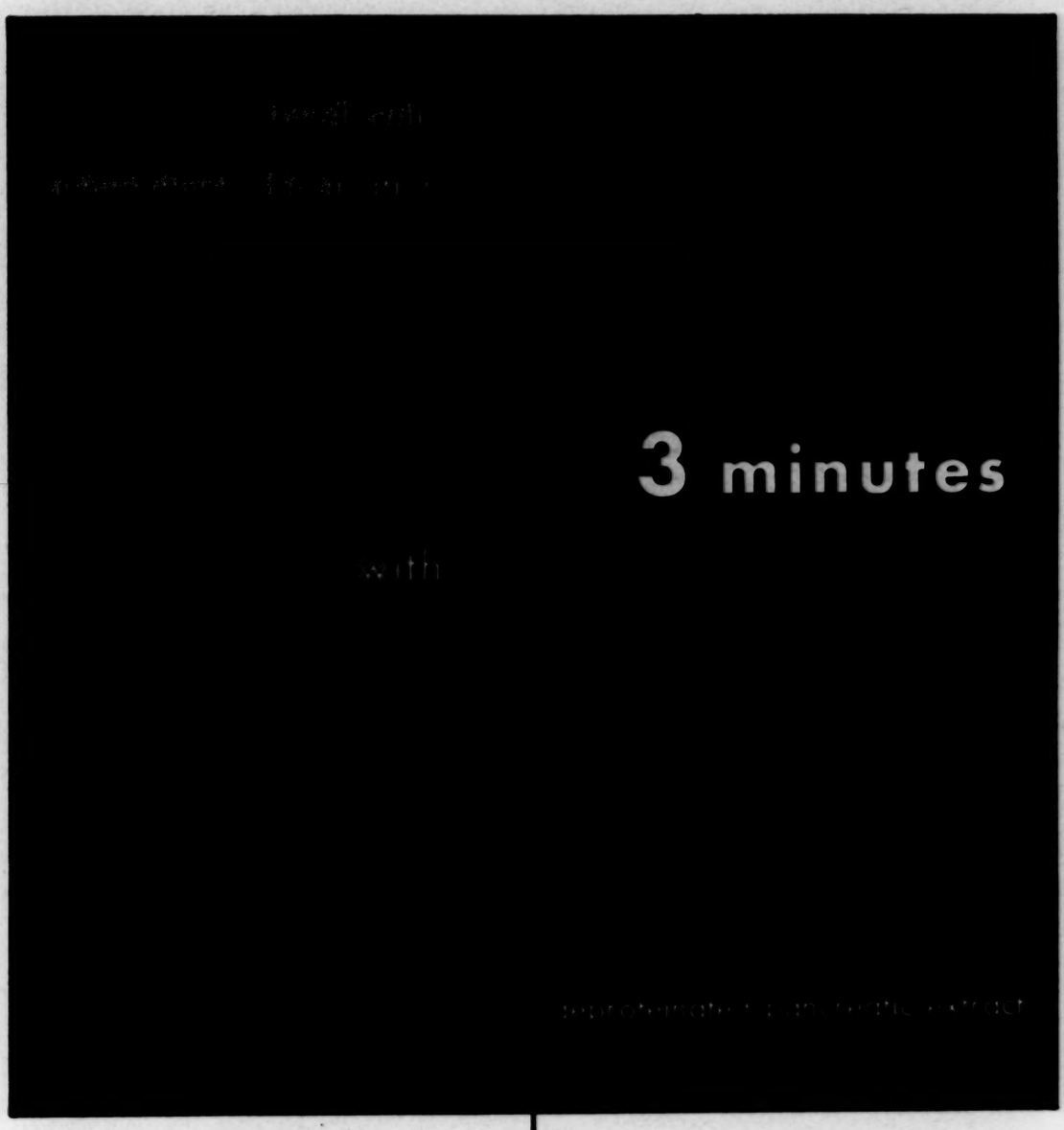
15 U. S. P. Injectable Units per cc. 1 cc., 5 cc., and 10 cc. rubber-capped vials. A highly refined and concentrated preparation for massive dosage.

Solution Liver Extract—Oral
45 cc. equal 1 U. S. P. Oral Unit. A readily assimilable and therapeutically effective preparation for use when the oral route is indicated or preferred.

Liver Extract Concentrate—Capsules
9 capsules equal 1 U. S. P. Oral Unit. Odorless, tasteless. Sealed gelatin capsules in boxes of 50, 100.

ARMOUR *Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS



Smooth muscle spasm—immediate cause of pain in ureteral and renal colic and intermittent claudication—is relaxed within *3 minutes* by intramuscular injection of DEPROPANEX *deproteinated pancreatic extract.*

This safe, effective antispasmodic is particularly useful in controlling spasm caused by calculus, stricture or instrumentation. Moreover, it is effective also in facilitating retrograde pyelography and ureteral dilatation, for treatment of spastic ureteritis, and for relief of primary dysmenorrhea.

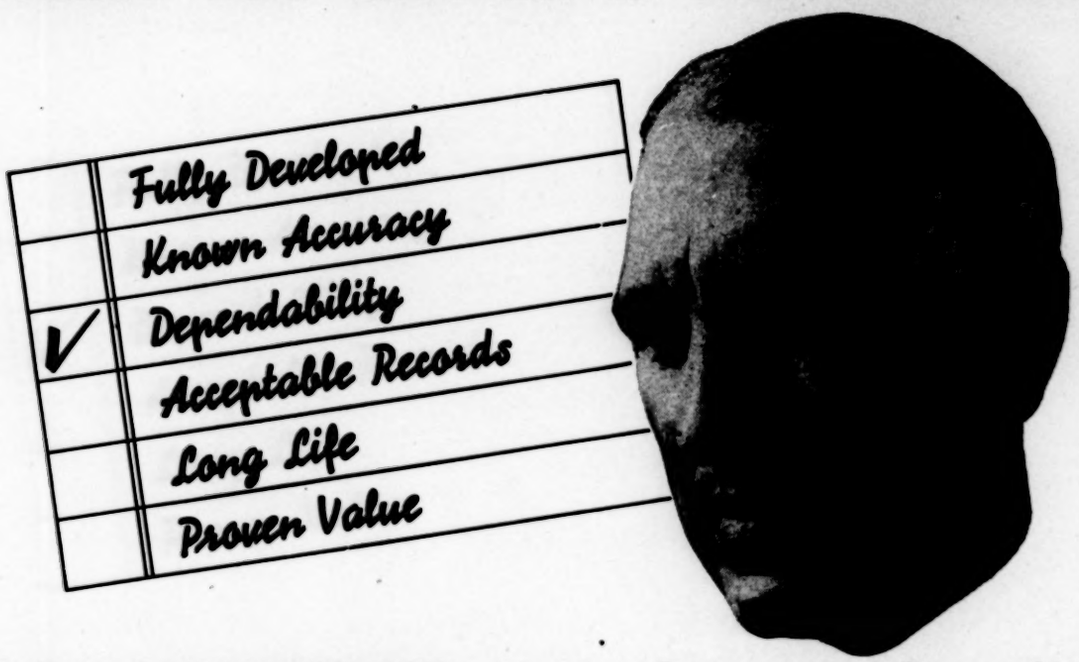
DEPROPANEX *deproteinated pancreatic extract* is entirely nontoxic and free from physiologically significant amounts of histamine, insulin and acetylcholine. Supplied in 10-cc. rubber-capped vials. Sharp & Dohme, Philadelphia 1, Penna.

SHARP & DOHME

deproteinated pancreatic extract

Depropanex

WHAT YOU GET IN A CAMBRIDGE



"My CAMBRIDGE *never lets me down!*"

In over a quarter of a century of exacting service, Cambridge Electrocardiographs have proven their day-by-day dependability. Cardiologists everywhere know from experience that their Cambridge Electrocardiographs will give unfailing service, produce accurate records . . . at any time . . . any place.

The "Simpli-Trol" Portable Model is contained in one case, 8" x 10" x 19", and weighs only 30 lbs. Mobile and Research Models are also available. Line operation from any house lighting outlet eliminates battery nuisance. Any model may be arranged to record heart sounds, pulse, and electrocardiogram simultaneously.

The dependability of the CAMBRIDGE is the result of the uncompromising combination of sound fundamental principles, exacting engineering and precision construction by skilled instrument makers. Continuous improvements have made today's instruments simple, convenient to operate, compact and light in weight, as well as accurate and dependable. Upkeep is negligible.

When you select a Cambridge Electrocardiograph, Doctor, you choose an instrument that you can depend upon for your lifetime in practice. You can afford no less... nor can you buy more.

Send for descriptive literature

CAMBRIDGE INSTRUMENT CO., INC., 3758 Grand Central Terminal, New York 17

Pioneer Manufacturers of the Electrocardiograph

Chicago 12, 2400 W. Madison St. Philadelphia 4, 134 S. 36th St. Cleveland 15, 1720 Euclid Ave.

CAMBRIDGE ELECTROCARDIOGRAPH

AND THE CAMBRIDGE ELECTROKYMOGRAPH PLETHYSMOGRAPH AMPLIFYING STETHOSCOPE
RESEARCH pH METER, BLOOD PRESSURE RECORDER LINDEMANN ELECTROMETER ETC.

Clear the airway

with

GLUCO-THRICIL®

antibiotic nasal decongestant

GLUCO-THRICIL promotes prompt and sustained relief from the discomforts of nasal obstruction. Combining, in stable solution, the membrane-shrinking action of ephedrine with the non-sensitizing, high antibacterial activity of Tyrothricin, it increases nasal ventilation and minimizes the possibilities of bacterial invasion.

GLUCO-THRICIL's low tissue toxicity, its isotonicity and pH within the range of those of normal nasal secretions, and its low surface tension, permit wide clinical application in both prophylaxis and treatment.

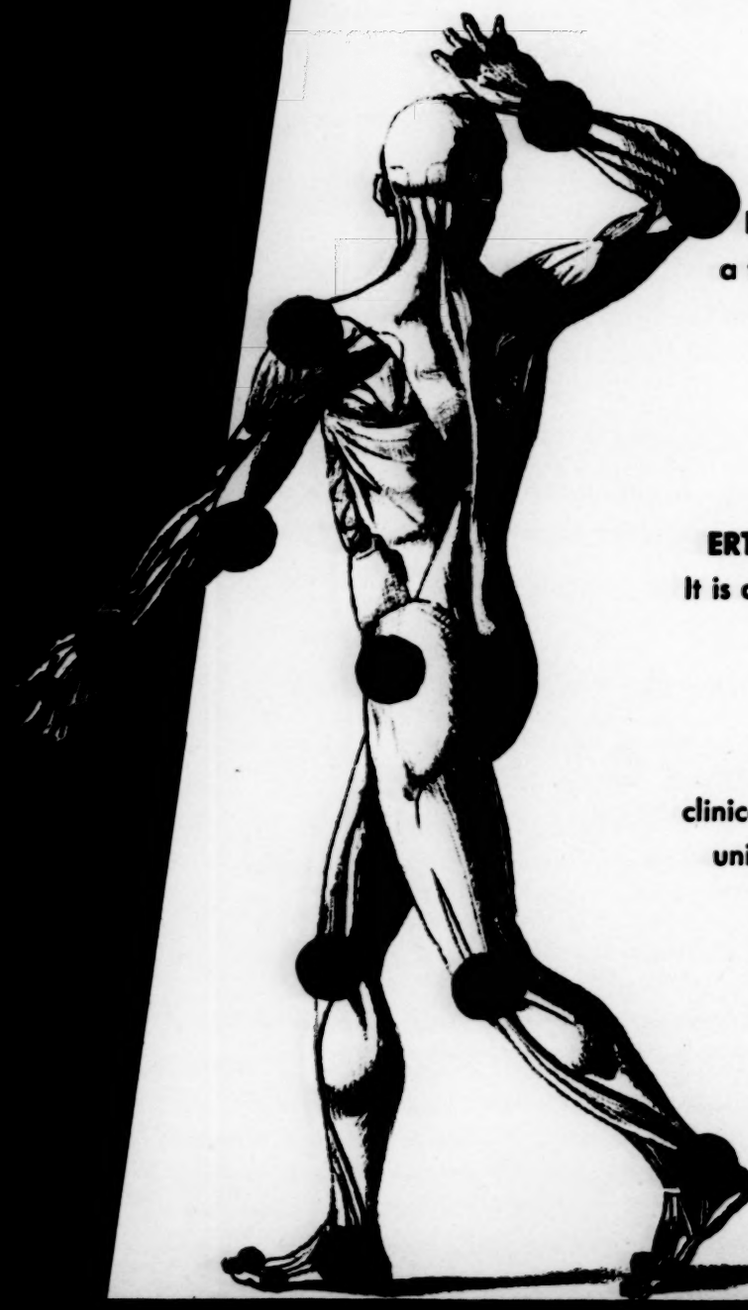
The head-low-lateral position is recommended for administration of GLUCO-THRICIL: adults, 2 to 4 drops in each nostril, three or four times daily; children, 1 to 2 drops in each nostril, three times daily. May also be given as spray or nasal pack.

GLUCO-THRICIL: 1-ounce bottles with dropper cap, and 1-pint bottle. Each fluidounce represents: ephedrine (as the lactate) 1%; Tyrothricin, 1:5000, in an isotonic dextrose solution containing cetyl trimethyl ammonium acetate as a solubilizing and stabilizing agent.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

MEDICAMENTA VERA · PD CO.

ERTRON



What it is:

ERTRON (Steroid Complex, Whittier) is a therapeutic agent of proved value in the management of chronic arthritis, with significant arthrokinetic effect—improved mobility of arthritic joints—in many cases.

ERTRON is of unique chemical composition. It is a complex mixture of activation-products derived from electrical activation of heat vaporized ergosterol.

ERTRON is relatively safe judged by clinical investigations in leading hospitals and universities over a period of thirteen years.

ERTRON Capsules: Each capsule contains 5 mg. of activation-products biologically standardized having an antirachitic activity of fifty thousand U.S.P. units. Bottles of 50, 100 and 500 capsules.

in arthritis

What it is not:

ERTRON® is not a panacea or specific designed to supersede medical, surgical or physiotherapeutic measures of acknowledged merit.

ERTRON is not to be confused with vitamin D products obtained by other methods (ultraviolet irradiation) or derived from other sources (fish liver oils).

ERTRON is not likely to produce serious untoward effects when administered under the physician's surveillance with proper observation of contraindications.

ERTRON Parenteral: Each ampule contains activation-products, in sesame oil, biologically standardized having an antirachitic activity of five hundred thousand U.S.P. units. Packages of six 1 cc. ampules

Nutrition
Research
Laboratories

The Long and Short of digitalis therapy!

With Digitaline Nativelle, cardiotonic influence usually becomes apparent within *three* hours. Full digitalization can be accomplished as rapidly as *six hours —instead of in days!*

Only such effectiveness brings the patient the desired, *quick relief* of air hunger and discomfort—and with virtual freedom from side effects. The physician will welcome the ease of administration as well as the considerably greater accuracy in therapy.

Simplicity of administration . . .

RAPID DIGITALIZATION . . . 1.2 mg. in equally divided doses of 0.6 mg. at three-hour intervals.

MAINTENANCE . . . 0.1 or 0.2 mg. daily depending upon patient's response.

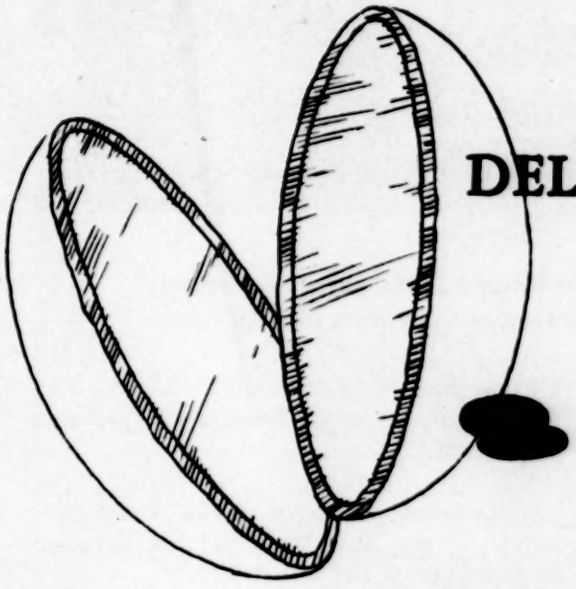
CHANGE-OVER . . . 0.1 or 0.2 mg. of Digitaline Nativelle may advantageously replace present maintenance dosage of 0.1 gm. or 0.2 gm. of whole leaf.

Current references and comprehensive brochure "Management of the Failing Heart" available on request. Also, if you wish, we will send a full digitalizing dose. Simply address Research Division, Varick Pharmacal Company, 75 Varick Street, New York 13, N. Y.

Digitaline Nativelle

. . . active glycoside of digitalis purpurea (*digitoxin*)

PYRIBENZAMINE *in a NEW form . . .*



DELAYED ACTION
TABLETS

FOR NIGHT-LONG ALLERGIC RELIEF

Many allergic patients may now receive symptomatic relief throughout the night. Delayed action tablets of Pyribenzamine are protected by a special coating so that the drug is not released for absorption until approximately the time an uncoated tablet ceases to be effective (4 to 6 hours). Sufferers from hay fever, urticaria, or atopic dermatitis can usually obtain night-long relief by taking one uncoated tablet of Pyribenzamine with one delayed action tablet at bedtime.

Pyribenzamine; scored tablets 50 mg., elixir 5 mg. per cc. (Council Accepted)

- Pyribenzamine delayed action tablets 50 mg. (Not Council Accepted)

Ciba

PYRIBENZAMINE (brand of tripelennamine) Trade Mark Reg. U.S. Pat. Off.

CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

Significant Clinical Results in Certain Allergic Disorders

Extensive clinical investigation has established that:

★ ***Neo-Antergan*** **produces EFFECTIVE SYMPTOMATIC RELIEF in a high percentage of patients with certain allergic manifestations.**

★ **This remarkably efficient histamine antagonist possesses a WIDE MARGIN OF SAFETY.**

★ **Patients who fail to respond satisfactorily to other therapeutic methods may receive effective symptomatic relief from *Neo-Antergan*.**

The majority of patients readily tolerate the average therapeutic dose of 50 mg., two to four times daily. In some cases, 25 mg., two to four times daily, will afford appreciable symptomatic relief with minimal side effects. Side reactions, when they occur, have been found to be generally mild and transient. Discontinuance of treatment has been necessary only in *approximately 1½ per cent* of patients.

Your local pharmacy stocks Neo-Antergan in 25-mg. and 50-mg. tablets, supplied in packages of 100 and 1,000.

INDICATIONS: HAY FEVER • PRURITUS • URTICARIA • VASOMOTOR RHINITIS • ATOPIC DERMATITIS ECZEMA • ALLERGIC DRUG REACTIONS • and certain other allergic disorders.

NEO-ANTERGAN MALEATE

Brand of Pyrilamine Maleate

(N-p-methoxybenzyl-N′,N′-dimethyl-N-α-pyridyl-ethylenediamine maleate)

MERCK

MERCK & CO., Inc.

Manufacturing Chemists

RAHWAY, N. J.

New Form of Procaine Penicillin for Aqueous Injection

All the advantages of Procaine Penicillin in Oil . . .
none of the disadvantages

WYCILLIN

TRADEMARK

Crystalline Procaine Penicillin G
for Aqueous Injection Wyeth

Wycillin provides a stable aqueous suspension of the new chemical compound, crystalline procaine penicillin G. It brings to the service of the physician for the first time a preparation for aqueous injection which avoids the dangers, pain and irritation of oil and wax and has many distinct superiorities:

No oil—avoids danger of oil embolism and oil sensitivity.

No wax—no pain at site of injection—no danger of tissue damage.

Stable—Wycillin is supplied in dry form. It is the first penicillin preparation for aqueous injection which when reconstituted with water does not require refrigeration.

No more plugged needles—Wycillin can be injected without drying needle or syringe—any method of sterilizing may be used.

Therapeutic effectiveness—a single injection of 1 cc. (300,000 units) maintains effective 24 hour blood levels in nearly all cases.

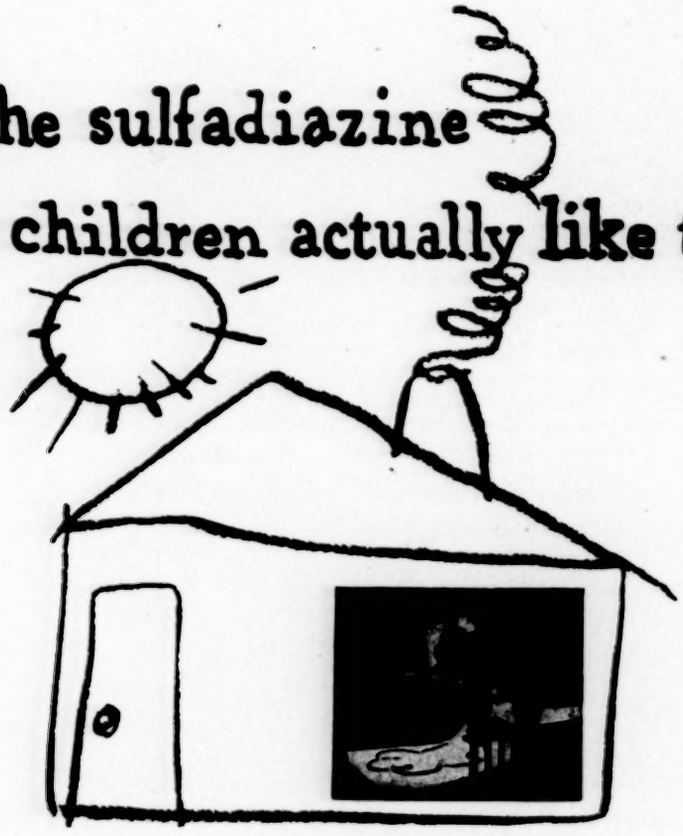
Wycillin is used in the same dosage and in the same conditions as Procaine Penicillin in Oil or Penicillin in Oil and Wax.

Druggists throughout the United States have received supplies of Wycillin by air mail. If you have any difficulty in obtaining it, please let us know so we can see that you are supplied.

Wyeth®

WYETH INCORPORATED PHILADELPHIA 3, PA.

Here's the sulfadiazine that children actually like to take



Exceptionally flavorful, this fluid sulfadiazine is the ideal dosage form for your young patients. They take it willingly because it tastes good. And it relieves tired parents and busy nurses of the chore of crushing tablets and coaxing a sick child to swallow an unappealing mixture.

Important, too, is the more rapid absorption of Eskadiazine. Flippin and associates* have established that desired serum levels are attained in two hours, rather than the six hours required for sulfadiazine in tablet form.

Smith, Kline & French Laboratories, Philadelphia

Eskadiazine

*Am. J. M. Sc. 210:141, 1945

the outstandingly palatable fluid sulfadiazine for oral use

Time and tide

in modern diuretic therapy

Timely injections of MERCUHYDRIN combat the rising tides of edematous fluid and check recurrences by mobilizing water-binding sodium and stimulating its urinary excretion.

MERCUHYDRIN facilitates the recommended frequent-dosage schedules[2] of modern diuretic therapy. Convenience, high local tolerance[3, 4, 5] and increased safety of the intramuscular route[6] foster the maintenance of a relatively constant level of body fluid by repeated injections,[7] thus sparing patients the distressing consequences of intermittent massive diuresis.

Prompt inauguration of MERCUHYDRIN diuresis in cardiac patients exhibiting nocturnal dyspnea, orthopnea, pulmonary râles, cardiac asthma and insomnia relieves discomfort and prolongs life.[8]

MERCUHYDRIN®

well tolerated locally, a diuretic of choice

Administration prior to or concurrently with digitalization avoids driving the faltering heart against an accumulated fluid burden and prevents the overdigitalization which may occur when postponed diuretic therapy mobilizes previously administered cardioactive glycosides from edema fluid.[9]

DOSAGE: 1 cc. or 2 cc. intramuscularly or intravenously, given daily, or as indicated, until a weight plateau is attained. Subsequently the interval between injections is prolonged to determine the maximum period permitted to intervene between maintenance injections.

PACKAGING: MERCUHYDRIN (meralluride sodium) is available in 1 cc. and 2 cc. ampuls.

BIBLIOGRAPHY: 1. Reeser, P. B. and Burch, G. E.: Proc. Soc. Exper. Biol. & Med. 63:343, 1946. 2. Conferences on Therapy, New York State J. Med. 43:2306, 1943. 3. Finkelstein, M. B. and Smyth, C. J.: J. Michigan State Med. Soc. 45:1618, 1946. 4. Modell, W., Gold, H., Clarke, D. A.: J. Pharm. & Exper. Therap. 84:284, 1945. 5. Jezer, A. and Gross, H.: Med. Clin. North America, Sept. 1947, p. 1301. 6. Wexler, J. and Ellis, L. B.: Am. Heart J. 27:86, 1944. 7. Conferences on Therapy, New York State J. Med. 44:280, 1944; 46:62, 1946. 8. Donovan, M. A.: New York State J. Med. 45:1756 (Aug. 15) 1945. 9. Levine, S. A.: Clinical Heart Disease, 2nd ed., Philadelphia, W. B. Saunders, 1942, p. 334.

Lakeside Laboratories, INC., MILWAUKEE 1, WISCONSIN

"...there are no standards which apply to all foods;
...there are no standards which apply to all individuals."

F. L. ADAIR
J. A. M. A. 128:344, 1945

To help meet the differing nutritional needs seen from day-to-day, and from patient-to-patient, the following mixed-vitamin preparations are recommended:

For the sick patient . . .

THERAPEUTIC FORMULA SQUIBB

VITAMIN CAPSULES

. . . because "of patients hospitalized for all reasons, two-thirds are afflicted with malnutrition";[1] and because "it is necessary to repair or rebuild these inroads in the nutritive system"[2], if the patient is to be restored to health and strength.

Squibb Therapeutic Formula provides truly *therapeutic dosages* of all the vitamins known to be essential for human nutrition.

Or, also for the sick . . .

BASIC FORMULA SQUIBB

VITAMIN TABLETS

. . . because "severe deficiencies of the water-soluble vitamins are much more common than those of the fat-soluble group . . ."[4]

Squibb Basic Formula provides the four critical water-soluble vitamins in *therapeutic dosages* – for cases in which treatment is not to be unduly prolonged and the fat-soluble vitamins may not be indicated.

For the well patient . .

SPECIAL FORMULA SQUIBB

VITAMIN CAPSULES

. . . because "one attack of nutritional disease seems to predispose to recurrences. Consequently, rehabilitation insists upon follow-up studies of the patient to insure his continued well-being."[3]

Squibb Special Formula provides *maintenance dosages* of the known essential vitamins.

For therapy in certain macrocytic anemias, so frequently associated with mixed vitamin deficiencies, Squibb Therapeutic Formula, modified with folic acid, is now available. When prescribing folic acid, specify – Squibb Therapeutic Formula Modified.

Bibliography: (1.) M. Record 160:394 (July) 1947. (2.) Conferences on Convalescent Care, New York, N. Y. Acad. Med. 1940, pp. 15-35. (3.) Pennsylvania M. J. 50:1318 (Sept.) 1947. (4.) M. Clin. North America, New York Number: 794 (May) 1945.

Flo-Cillin

Crystalline Procaine Penicillin G in Oil

(300,000 units per cc.)

With Aluminum Monostearate 2%

Bristol's new penicillin repository product provides these unique features:

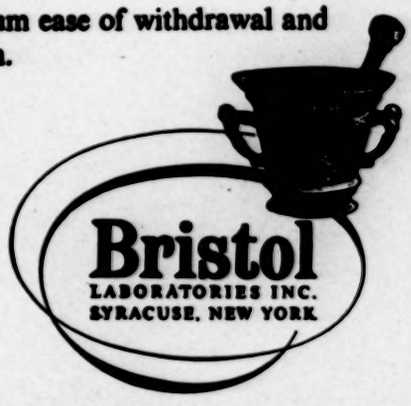
1 A free-flowing, liquid product which remains constantly in suspension.

2 Exceptionally sustained concentrations of penicillin in the blood.

3 Complete uniformity of dosage.

4 Maximum ease of withdrawal and injection.

Available through your usual source of supply in vials containing ten 1 cc. doses of 300,000 units per cc.



to revive normal interest and activity

'Dexedrine' is of unequalled value for the depressed patient.

Not only does Dexedrine produce striking improvement in mood and outlook—but, because of the unique "smoothness" of its action, it spares the patient the disturbing consciousness of "drug stimulation."
Smith, Kline & French Laboratories, Philadelphia

Dexedrine*

Sulfate elixir tablets

the central nervous stimulant of choice (*dextro-amphetamine sulfate, S. K. F.*)

*T.M. REG. U.S. PAT. OFF.

"... dienestrol is a particularly useful estrogen ..."

Wiles

IMPORTANT INDICATIONS

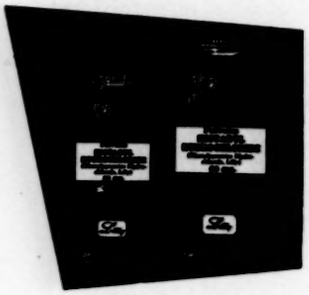
FOR

HISTADYL HYDROCHLORIDE

(Thenylpyramine Hydrochloride, Lilly)

- *Pollinosis*
- *Food and drug allergy*
- *Atopic dermatitis and eczema*
- *Chronic urticaria*
- *Allergic cough*

'Histadyl Hydrochloride' (Thenylpyramine Hydrochloride, Lilly) is a potent antihistaminic which is relatively free from side actions. Literature is available to physicians upon request.



ELI LILLY AND COMPANY

INDIANAPOLIS 6, INDIANA, U. S. A.

The American Journal of Medicine

VOL. IV JUNE, 1948 No. 6

Editorial

Pain and Dystrophy in the Extremities

In the last few years there has been renewed interest in the syndromes of pain and dystrophy of the extremities first described by Mitchell, Paget and Sudeck.[1–3] These studies present many new descriptive terms,* in evidence that a number of clinical pictures have important features and probably mechanisms in common; and, what is more important, new contributions to underlying physiologic mechanisms.

The most important contributions to the basic physiologic fault have dealt with new concepts of transmission of nerve impulses in previously unrecognized pathways. Skoglund and his associates[4] have shown by standard physiologic methods that injury to a nerve may establish artificial synapses and result in the transfer of nerve impulses from motor to sensory fibers. Doupe and his associates[5] independently suggested that in causalgia the essential lesion is one which permits the passage of impulses in the injured nerve from sympathetic to sensory fibers in which travel centrally, results in pain while distal transmission as antidromic impulses might have vasomotor and trophic effects. They presented this idea mainly as an explanation of pain.

The concept of the pathologic synapse as the essential fault in the pain of causalgia explains remarkably well its distinctive characteristics: initiation by trauma to nerves, relief by block of sympathetics, lack of relief after nerve block distal to point of injury and the peculiarity that causalgic pain is made worse by a number of reactions known to increase impulses in sympathetic nerves of the extremities, such as excitement, a painful pin prick in unaffected parts, a deep breath and adjustments of temperature regulation. Extreme hyperesthesia of an extremity when touched by the examiner, although the patient touches the part without discomfort, is explained in terms of autonomic system reaction to fear rather than as an expression of malingering. In view of the demonstration by Granit and Skoglund that nerve injury may establish an artificial synapse between motor and sensory nerves, it may well be true, as suggested by these workers, that pain on movement may arise in part from abnormal transfer of nerve impulses rather than from actual movement. The pain of phantom limb may be explained by synapses established in a neuroma.

There has been a tendency to assume that exacerbation of causalgic pain with emotional excitement is merely a manifestation

[1] MITCHELL, S. W., MOREHOUSE, G. R. and KEEN, W. W. Gunshot Wounds and Other Injuries of Nerves. Chap. 4. Philadelphia, 1864. J. B. Lippincott.

[2] PAGET, S. *M. Times & Gaz.*, London, p. 531, March, 1864.

[3] SUDECK, P. Ueber die akute entzündliche Knochenatrophie. *Arch. f. klin. Chir.*, 147–156, 1900.

* Acute atrophy of bone, traumatic atrophy of bone, traumatic angiospasm, chronic traumatic edema, peripheral trophneurosis, reflex nervous dystrophy, reflex arterial spasm, chronic segmental arterial spasm, reflex dystrophy of the extremities, trophic edema, traumatic osteoporosis, état physiopathique of Vulpian. The multiplicity of descriptive terms currently in use for Mitchell's causalgia and Sudeck's atrophy indicates that none is satisfactory.

[4] GRANIT, R., LEKSELL, L. and SKOGLUND, C. R. Fibre interaction in injured or compressed region of nerve. *Brain*, 76: 125–40, 1944.

[5] DOUPE, J., CULLEN, C. H. and CHANCE, G. W. Post-traumatic pain and the causalgic syndrome. *J. Neurol. Neurosurg. & Psychiat.*, 7: 33–48, 1944.

of the patient's neurotic personality. The concept of the pathologic synapse throws light on how lesions of peripheral nerves may put severe stress upon personality. The idea that nerve lesions may contribute to personality disorders need not blind us to the fact that in some cases of chronic pain the principal etiologic factor lies in faulty personality organization. The study of patients with pain and dystrophy of extremities offers a fruitful field for collaboration among psychiatrists, internists and surgeons.

Some of the patients studied by Doupe and his associates, with pain differing somewhat from the pain of classic causalgia, were relieved by nerve block distal to the point of injury. Because of these cases the term dystrophic pain has been introduced with the concept that abnormal transfer of nerve impulses is believed to take place in the periphery rather than in nerve trunks and that the neurologic lesion is a result of defective local nutrition. For those patients Doupe and his associates reverse the usual concept of cause and effect and suggest that pain is a consequence of trophic changes rather than that trophic changes spring from a painful disorder. A mechanism of this sort deserves especial attention by internists because disease of the arteries and veins in the extremities is so common.

There is still great confusion about the mechanisms responsible for local faults of nutrition which are frequently associated with severe and persistent pain in extremities. Such trophic lesions may occur in the absence of pain and it is difficult to quantitate the effects of disuse. There is no doubt that nervous system lesions at different levels may be responsible for vasomotor and trophic disorders: edema, glossy skin, blisters, ulcers, eczema, muscle weakness and atrophy of bone. Bilateral prefrontal lobotomy is frequently followed by pain and edema of the feet and legs; the skin is dry, warm and tender and blisters tend to appear which sometimes form ulcers.[6] There is a wide difference of opinion as to the meaning of vasomotor disorders associated with pain and dystrophy in extremities. Miller and de Takats[7] have studied this aspect of the problem with unusual thoroughness and are of the opinion that abnormalities of blood flow are of great importance in the production of trophic disorders. Doupe and his associates minimize the peculiarities of blood flow in extremities with primary injury to damaged nerves, but when there is disease of blood vessels they emphasize the importance of nerve injury caused by defective blood flow. Reider,[8] whose work is difficult to evaluate because of inadequate details of method, is convinced that hyperemia of the bone marrow is regularly associated with bone atrophy.

The distribution of pain and hyperesthesia in the extremities frequently does not coincide with the area supplied by the injured nerve. Ray and Wolff[9] studied patients who had had a high thoracic section of the ventral-lateral portion of the cord on one side by applying an intense, noxious stimulus to an analgesic area. The individuals perceived pain on the normally innervated side of the body with such distribution as to indicate that the nerve impulse had spread to the opposite side and to adjacent segments of the cord.

There is good evidence that in some cases of pain and dystrophy we are dealing with a true vicious cycle in which pain induces more pain and tissue injury may favor further local malnutrition. The success in breaking the cycle by procaine injections of sympathetic nerves is frequently spectacular and the benefits outlast the local effect of the drug. This form of therapy deserves earlier and more frequent use in syndromes of severe pain in the extremities.

ROY H. TURNER, M.D.

[6] ZIEGLER, L. H. and OSGOOD, C. W. Edema and trophic disturbances of the lower extremities complicating prefrontal lobotomy. *Arch. Neurol. & Psychiat.*, 53: 262, 1945.

[7] MILLER, DONALD S. and DE TAKATS, GEZA. Post-traumatic dystrophy of the extremities (Sudeck's atrophy). *Surg., Gynec. & Obst.*, 75: 558–582, 1942.

[8] REIDER, W. Die akute Knochenatrophie. *Deutsche Ztschr. f. Chir.*, 248: 269, 1936.

[9] RAY, BRONSON S. and WOLFF, H. G. Studies on pain. *Arch. Neurol. & Psychiat.*, 53: 257–61, 1945.

Clinical Studies

Dynamics of the Left Auricle in Mitral Valve Lesions*

Fluorocardiographic Study

ALDO A. LUISADA, M.D. *and* FELIX G. FLEISCHNER, M.D.
Boston, Massachusetts

THE effects of mitral valve lesions on the left auricle have been studied by numerous authors using different methods. The fact that in mitral insufficiency blood regurgitates from the left ventricle into the left auricle during ventricular systole was first studied by auscultation. The clinicians of the last century first connected the apical systolic murmur with mitral regurgitation. The observation of a visible and palpable systolic thrust on the right side of the chest due to the expansion of a tremendously dilated left auricle, however, is comparatively recent (Dressler,[1] Ungerleider and Gubner[2]). Introduction of a compressible balloon and a sound into the esophagus permitted the tracing of volume changes of the left auricle (esophagocardiograms). Taquini[3] and Puddu and Sibilla[4] described a positive wave of short duration at the beginning of ventricular systole in cases of mitral insufficiency.

More accurate observations of motor changes of the left auricle have been made roentgenologically. Fluoroscopy may permit observation of a systolic expansion of the left auricle, especially if the esophagus is filled with barium. Roentgenkymography yielded characteristic records of the left auricle in either of the following conditions: (1) In cases in which the left auricle was so markedly enlarged that it formed a major portion of either the right or left cardiac silhouette permitting its pulsation to be recorded in the posteroanterior view and (2) in other cases in which the pulsations of the left auricle were best recorded in the right or left oblique position with the esophagus filled with barium.

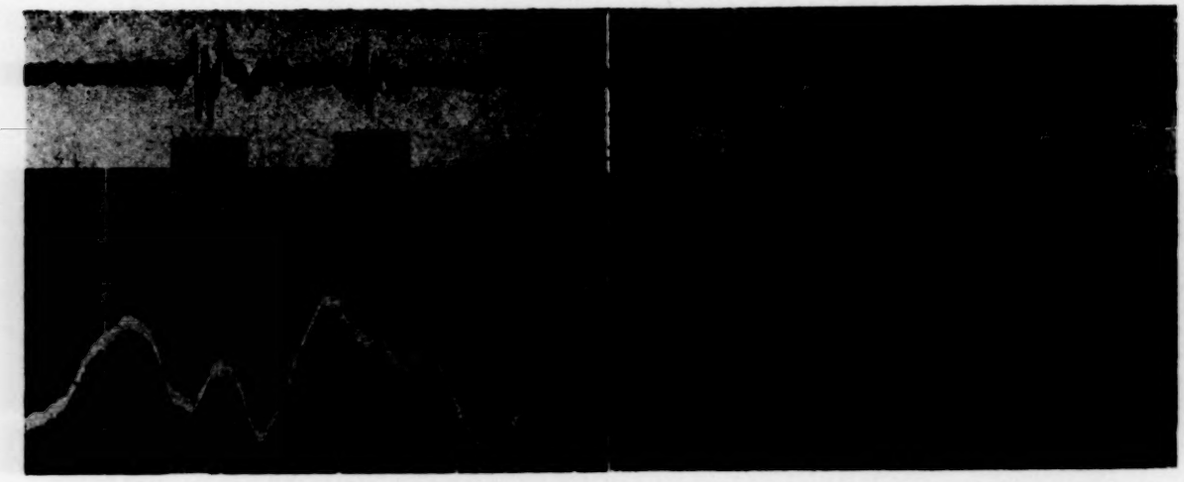
Although various observations have been reported in scattered publications and textbooks of roentgenology (Cignolini,[5] Roesler,[6] Gubner and Ungerleider[2] and Schwedel[7]), the most thorough kymographic study of the left auricle was published only recently by Heim de Balzac and Pannier.[8]

This paper will discuss the use of fluorocardiography in the study of the dynamics of the left auricle in mitral valve lesions. It is believed that fluorocardiography provides the most accurate tracings and we have utilized it in an investigation of all such cases coming under our observation.

TECHNIC

Henny, Boone and Chamberlain[9,10] described a roentgenologic method which they called electrokymography. A modification of this technic (Luisada, Fleischner and Rappaport[11]) has been employed in this study. We proposed the more descriptive term of *fluorocardiography* which will be used in this presentation. A Sanborn apparatus for fluorocardiography connected with a Stethocardiette has been used in order to record simultaneously the cardiac sounds and the pulsations of the various components of the cardiac silhouette. The

* From the Medical Service and the Department of Radiology of the Beth Israel Hospital, Boston, Mass.



A B

FIG. 1. Tracings of the left auricle in two normal male subjects aged twenty-two; right oblique position. A, a deep negative ventricular wave follows the auricular wave; B, a sharp negative auricular wave is present; the ventricular wave is less marked; *a*, indicates the auricular wave.

phonocardiograph was used not only as timer but also to study the heart sounds and murmurs. The technic used has been described in detail in a previous paper.[11] The present study deals only with observations of the left auricle.

This study includes twenty-seven examinations made on clinical patients. At first only patients definitely diagnosed by clinical means were studied; then, having observed a series of what were thought to be characteristic tracings, we also studied a few patients in whom the diagnosis was not established by ordinary clinical methods. All the patients studied included five with combined mitral and aortic lesions of rheumatic etiology; ten with double mitral defects of rheumatic etiology; three with mitral insufficiency and no clinical evidence of stenosis; two with mitral stenosis and no clinical evidence of regurgitation; two with complex cardiac lesions (probably of both rheumatic and congenital nature; one of them had Lutembacher's syndrome); one with arteriosclerotic heart disease with evidence of mitral regurgitation (apical systolic murmur) and four with clinical diagnosis of interventricular septal defect and a loud systolic murmur.

All patients were studied by means of physical examination, electrocardiography, phonocardiography and roentgenology before the fluorocardiographic study was undertaken. In most of the patients the three following sitting positions were employed: (1) The contour of the left auricular appendage was traced with the patient in a posteroanterior position, rotated 10 degrees to the left anterior oblique; (2) the contour of the left auricle was traced in the left anterior oblique as well as the right anterior oblique and (3) in addition, a densogram of the left auricle in one of the oblique positions was recorded in some of the patients.

OBSERVATIONS

As described in a previous paper[12] the tracings recorded over the left auricle in normal subjects present a typical pattern (Fig. 1) consisting of: (1) A sharp, presystolic, negative wave whose trough coincides with the initial vibrations of the first sound. (2) A smaller negative wave during ventricular systole. (3) A less constant, early diastolic collapse which may merge with the following presystolic wave (especially if there is tachycardia). An upward wave, occurring during the first sound, separates the presystolic from the systolic negative wave. The ascending limb of the latter often shows a gentle slope during late systole, due to the gradual filling of the auricle, and reaches its maximum height at the end of the second sound when a specific vibration

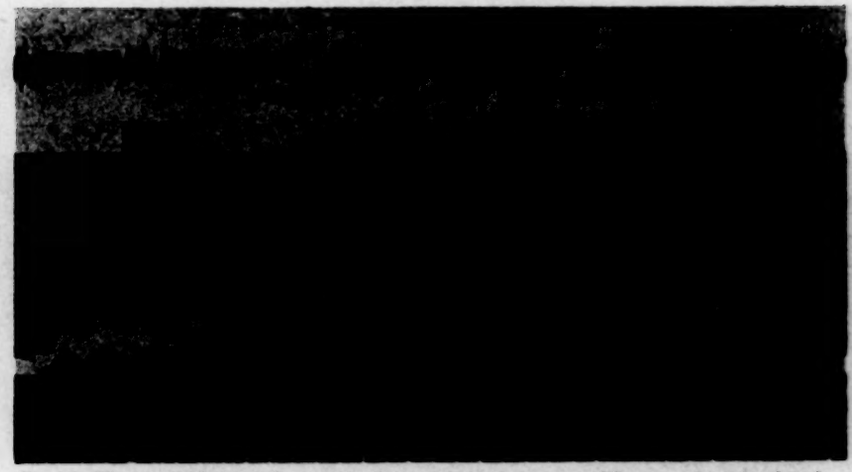


FIG. 2. Tracing of the left auricle in a thirty-two year old woman; mitral valve lesion; small auricular wave (*a*) followed by positive plateau during ventricular systole.

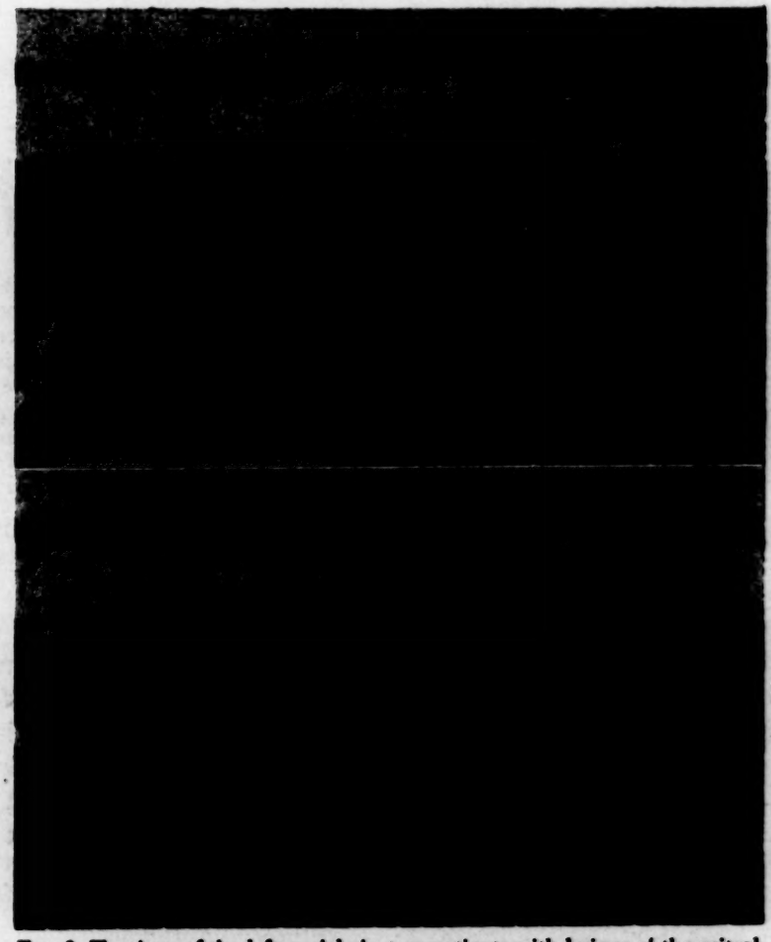
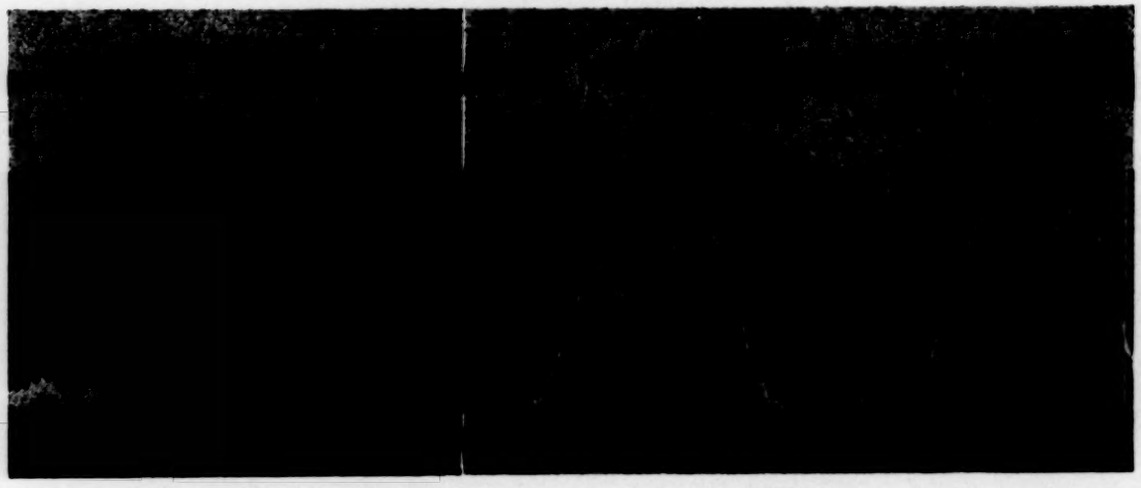


FIG. 3. Tracings of the left auricle in two patients with lesions of the mitral valve and sinus rhythm. A, a fifteen year old girl with a slight mitral lesion; long systolic murmur; deep negative auricular wave followed by positive plateau during ventricular systole. B, a thirty-five year old woman with mitral and aortic lesions; deep negative auricular wave followed by positive plateau during ventricular systole. Both tracings were recorded in the left anterior oblique position.



A B

FIG. 4. Tracings of the left auricle in left oblique position in patients with mitral valve lesion and auricular fibrillation; high positive plateau; no evidence of auricular contraction. A, a forty-two year old woman with no systolic murmur audible and an opening snap of the mitral valve; B, aortic and mitral lesions.

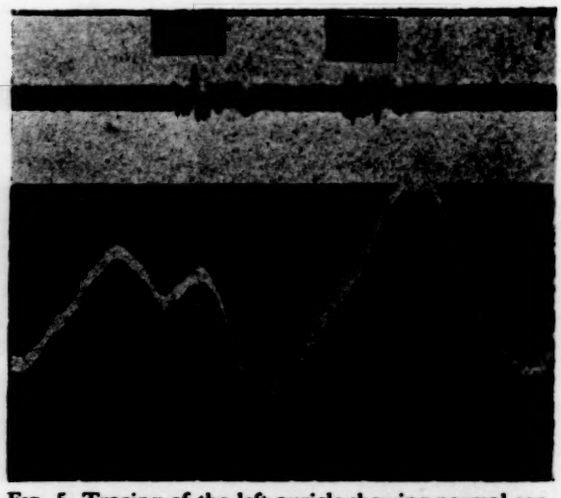


FIG. 5. Tracing of the left auricle showing normal configuration in a man of twenty-four with clinical diagnosis of interventricular septal defect.

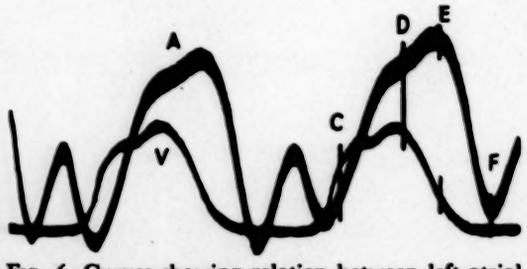


FIG. 6. Curves showing relation between left atrial volume (A) and left ventricular pressure (V) during experimental mitral regurgitation. Atrial volume increases insignificantly during isometric contraction ending at C, augments markedly during ventricular ejection terminating at D, and is continuous during isometric relaxation terminating at E. (From Wiggers' Physiology in Health and Disease. Courtesy of the author and of the Lea and Febiger Co.)

marks the opening of the mitral valve (Rappaport and Sprague).[13]

Patients with Mitral Valve Lesions without Auricular Fibrillation. This group included sixteen observations made on thirteen patients; in fifteen observations there was a normal sinus rhythm and in one, nodal rhythm. In ten of the patients a typical pattern was observed which may be analyzed as follows: (1) The presystolic negative wave, evidence of auricular contraction, is present. It may be small, irregular in shape or barely visible. (Fig. 2.) (2) During ventricular systole a flat positive wave shaped as a "plateau" is present. It is identical in shape and time relationship with that observed in patients with auricular fibrillation. (Fig. 3.)

The other three patients in whom a normal or nearly normal pattern was observed, were studied earlier and incompletely, i.e., only in one or two positions. Inasmuch as the aforementioned typical pattern does not necessarily present itself in all positions, the negative findings in these patients may be explained on this basis.

Patients with Mitral Valve Lesions and Auricular Fibrillation. This group included ten patients; in nine of them a typical pattern (Fig. 4) was observed which had the following characteristics: (1) Absence of the presystolic auricular wave and (2) presence of an abnormal positive wave

during ventricular systole. This has the form of a quadrangular or rectangular "plateau." It resembles tracings of intraventricular pressure as observed in animal experiments. If an early diastolic collapse is present, the tracing consists of the systolic plateau, the descending limb of which reaches further down as it merges with this collapse.

The only patient in whom this plateau was not found probably had a combined rheumatic and congenital lesion (mitral lesion plus septal defect) and, moreover, was not completely studied. Patients with an interventricular septal defect presented normal left auricular tracings. (Fig. 5.)

In summary, of twenty-three patients with mitral valvular disease, nineteen presented a typical pattern, differing from the normal, characterized by a positive plateau during ventricular systole. Correlation of the clinical diagnoses, the phonocardiographic findings and the fluorocardiographic tracings leads to the following conclusions: (1) Patients with mitral regurgitation or a double mitral lesion present a typical positive plateau which is especially prominent in the presence of auricular fibrillation. Associated aortic valvular lesions do not interfere with the appearance of the plateau. (2) Patients with mitral stenosis and no evidence of insufficiency (no systolic murmur) also present a typical plateau. (3) The plateau is typical in patients with sinus rhythm as well as in those with auricular fibrillation. (4) Patients clinically diagnosed as having an uncomplicated interventricular septal defect do not show any abnormal pattern in the tracing of the left auricle.

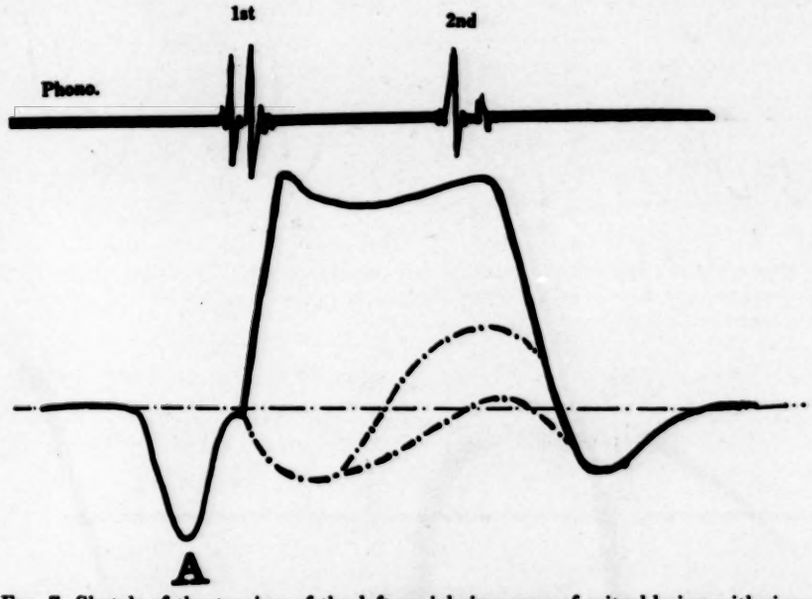


FIG. 7. Sketch of the tracing of the left auricle in a case of mitral lesion with sinus rhythm. The thin dotted line represents the arbitrary base line; the heavy dotted line represents normal tracings during ventricular systole.

COMMENTS

A typical fluorocardiographic tracing of the left auricle in patients with mitral valvular disease is produced by the continuous regurgitation of blood from the left ventricle into the left auricle during ventricular systole and is present in patients with sinus rhythm or auricular fibrillation. It consists of a rectangular, positive "plateau" resembling the classical experimental tracing of intraventricular pressure. This finding is not unexpected as it conforms with tracings obtained under experimental conditions of mitral regurgitation (Wiggers,[14] Fig. 6) and with clinical esophagocardiograms.[3,4] Moreover, it has been recorded by means of roentgenkymograms

made on patients with severe mitral lesions and a large left auricle (Cignolini,[5] Heim de Balzac and Pannier[8]).

It must be noted, however, that there are contradictions in these earlier studies. While the experiments on animals demonstrate

FIG. 8. Schematic tracings of the left auricle in mitral lesions: (1) normal; (2) initial neutralization of systolic collapse; (3) sinus rhythm, positive systolic plateau preceded by auricular contraction; (4) auricular fibrillation; positive systolic plateau, no trace of auricular activity.

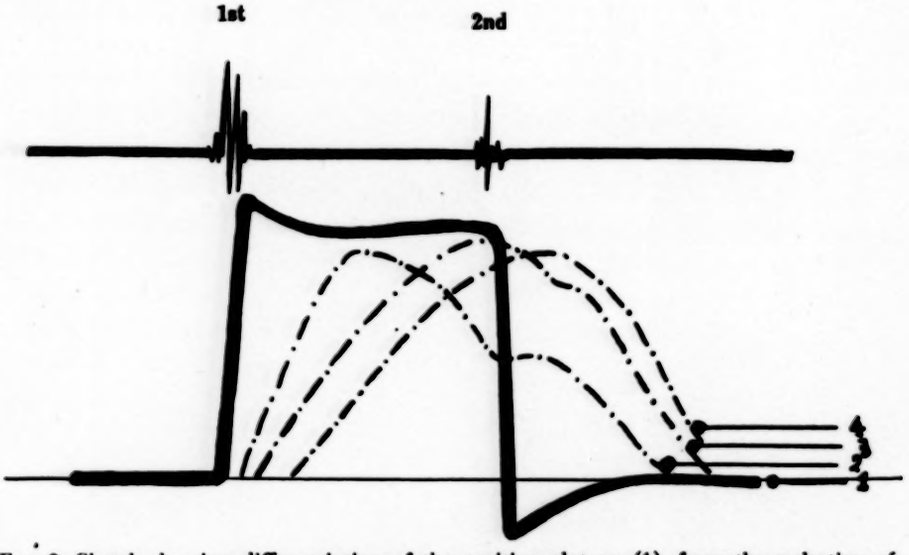


FIG. 9. Sketch showing differentiation of the positive plateau (1), from the pulsation of the pulmonary artery (2), of the hilar vessels (3) or the lung (4). Shape and relationship of the waves to the heart sounds are different.

regurgitation during and after the ejection period,[14] clinical esophagocardiograms showed regurgitation only at the beginning of systole.[4] In our tracings the regurgitation appears to be continuous, starting at the beginning of the tension period and continuing until after the opening of the mitral valve, i.e., after the end of the second sound. These findings, therefore, conform with the results of animal experimentation.

Classical roentgenkymography[8] demonstrated the occasional occurrence of severe regurgitation without a systolic murmur; the present studies confirm this. It has also been stated[8] that a loud systolic murmur due to a mitral lesion may be present without a typical plateau revealing the regurgitation. While this possibility cannot be ruled out, we have not found any satisfactorily studied case which confirms this observation. A typical pattern of regurgitation was found in all patients with mitral regurgitation in whom sinus rhythm was present, the left auricle was only moderately enlarged and no auscultatory or phonocardiographic evidence of mitral stenosis was present. (Fig. 8.)

Another abnormal feature may be found in tracings from patients with mitral lesions and sinus rhythm. (Fig. 2.) This consists of an abnormal form and depth of the auricular wave which is small, irregular and often difficult to visualize. This abnormality may be attributed either to slow

emptying of the left auricle because of severe mitral narrowing or to weak left auricular contraction caused by muscular damage in the left auricle.

By recording tracings of the left auricle in the oblique positions, superimposition of other structures, such as the pulmonary artery, the hilar vessels or the aorta is avoided. However, misinterpretation, possibly resulting from a summation of waves, can be obviated only by careful observation of the typical form of the specific waves and their relationship to the heart sounds. (Fig. 9.)

In conclusion, the fluorocardiogram of the left auricle in mitral valvular disease typically demonstrates a positive plateau (regurgitation) during ventricular systole. This is easily identified whenever there is auricular fibrillation and thus it may be of diagnostic value in the absence of an apical murmur. In patients with sinus rhythm the plateau wave is, however, of diagnostic value only if it is marked because of the absence of a definite base line. Hence only marked evidence of systolic elevation can be accepted as proof of a pathologic disorder. On the contrary, in the presence of moderate regurgitation the resulting elevation being only slight, it merely neutralizes the negative systolic wave or produces a slight rise which may be mistaken for the normal rise which occurs after the negative presystolic wave. (Figs. 8(*2*).) This finding, therefore, cannot be accepted as definite evidence of regurgitation.

Our findings indicate that in the patients studied mitral stenosis was always accompanied by regurgitation.

SUMMARY

Fluorocardiographic tracings of the left auricle were recorded in twenty-three patients with lesions of the mitral valve. The patients were about equally divided into two groups: one with sinus rhythm and the other with auricular fibrillation.

A typical pattern was found in nine of ten patients with fibrillation and in ten of thirteen of those with sinus rhythm. This consists of a positive *plateau* which is evidence of expansion of the left auricle during ventricular systole because of regurgitation.

A description of the distinctive features of this pattern is given.

Another variation, consisting of abnormalities in shape and depth of the presystolic auricular wave, is found in certain patients with sinus rhythm and is explained as the result either of severe narrowing of the mitral valve or structural lesion of the left auricular wall.

The practical diagnostic value of these graphic signs is discussed.

Possible existence of a pure mitral stenosis, not accompanied by mitral insufficiency, was not demonstrated in the present study.

REFERENCES

1. Dressler, W. Die Brustwandpulsationen. Wien, Maudrich. Also Clinical Cardiology, New York, 1942. Paul B. Hoeber.
2. Ungerleider, H. E. and Gubner, R. In Stroud's Diagnosis and Treatment of Cardiovascular Disease. Philadelphia, 1945. F. A. Davis Company.
3. Taquini, A. C. Exploración del Corazón por Via Esofágica. Buenos Aires, 1936. El Ateneo.
4. Puddu, V. and Sibilla, D. Soffio sistolico e insufficienza mitralica. *Cuore e circolaz.*, 26: 2, 1942.
5. Cignolini, P. Roentgenchimografia Cardiaca e Regmografia. Bologna, 1934. Cappelli.
6. Roesler, H. Clinical Roentgenology of the Cardiovascular System. Baltimore, 1943. Charles C. Thomas.
7. Schwedel, J. B. Clinical Roentgenology of the Heart. New York, 1946. Paul B. Hoeber.
8. Heim de Balzac, R. and Pannier, R. La radiokymographie cardiovasculaire: son utilité et son avenir. *Rev. belge sc. méd.*, 16: 1, 1945.
9. Henny, G. C. and Boone, B. R. Electrokymograph for recording heart motion utilizing the roentgenoscope. *Am. J. Roentgenol.*, 54: 217, 1945.
10. Henny, G. C., Boone, B. R. and Chamberlain, W. E. Electrokymograph for recording heart motion, improved type. *Am. J. Roentgenol.*, 57: 409, 1947.
11. Luisada, A. A., Fleischner, F. G. and Rappaport, M. B. Fluorocardiography (electrokymography). Note I: technical aspects. *Am. Heart J.*, 35: 336, 1948.
12. Luisada, A. A., Fleischner, F. G. and Rappaport, M. B. Fluorocardiography (electrokymography). Note II: observations on normal subjects. *Am. Heart J.*, 35: 348, 1948.
13. Rappaport, M. B. and Sprague, H. B. The graphic registration of the normal heart sounds. *Am. Heart J.*, 23: 591, 1942.
14. Wiggers, C. J. Physiology in Health and Disease. Philadelphia, 1944. Lea and Febiger.

Application of Microplethysmography to the Diagnosis of Patent Ductus Arteriosus and Coarctation of the Aorta*

RAYMOND S. MEGIBOW, M.D.† *and* SERGEI FEITELBERG, M.D.
New York, New York

RECENT developments in the surgical treatment of congenital heart disease have increased the practical importance of accurate anatomic diagnosis. This has been accomplished in part through development of more precise diagnostic criteria, and by use of specialized technics such as angiocardiography and direct catheterization of the heart.[1–4] In spite of these advances a small percentage of diagnostic errors persists.

It is the purpose of this report to relate observations made with a relatively new technic which led to the formulation of new diagnostic criteria in the preoperative study of patients with suspected patent ductus arteriosus and coarctation of the aorta.

METHODS

A direct ink recording microplethysmograph constructed by one of us (S. F.) has been utilized in all investigations. Exact details of construction are being published separately. Sensitivity is adjusted (by operating a control knob) to give a deflection of 10 to 20 divisions for a volume change of 20 mm.^{3}, full chart scale being equal to 50 divisions. Calibration may be checked manually at any time or automatically every ten minutes by introducing a volume change of 20 mm.^{3} into the system. The response of the pen is linear within 5 per cent over the 50 divisions. Noise level is less than ¼ division corresponding to a volume change of less than 0.25 mm.^{3} The frequency response is 5 cycles/second. The timing is automatic.

Whenever possible, the procedure was carefully explained to each patient beforehand. All tracings were obtained with the patient reclining comfortably on a couch. Psychic stimuli were kept at a minimum since they exert a profound effect upon the plethysmogram.[5] No effort was made to control temperature and humidity as long as the patient was not unduly chilled or warmed. Actual tracings were obtained by applying a plastic capsule to the fingers or toes according to a method previously described.[6] At least one recording was obtained on each patient preoperatively. In a number of instances the effects of nitroglycerin on the plethysmogram were observed. Whenever possible, plethysmograms were obtained after operation and were compared with the preoperative tracings. In a number of patients angiocardiograms were included in the diagnostic study. Electrocardiograms and in a number of instances phonocardiograms were also made available for study in these patients. All subjects underwent careful physical examination, particular attention being given to the character and transmission of the cardiac murmurs and to the arterial pressure.

RESULTS

The normal plethysmogram has been adequately described by Neumann et al.[7] (Figs. 1 and 2.) It is characterized by four distinct types of volume fluctuation: (1) a wave synchronous with the heart beat, (2) slower undulations which are induced by respiration and are more distinct in the fingers than in the toes, (3) much slower and larger volume changes, termed alpha

* From the Clinical Services and the Physics Laboratory of The Mount Sinai Hospital, New York, N. Y. Presented in part at the International Pediatric Congress August, 1947. Read in part by title at the meeting of the American Heart Association June, 1947.

† Fellow in Medicine, Rosenstock Memorial Foundation.

FIG. 1. Plethysmogram from finger of a normal subject. Note the sharp apex, the distinct dicrotic notch and the well developed respiratory fluctuations. (Ordinates equal 5 seconds. Calibration to left of each figure indicates a volume change of 20 mm^3).

waves, induced apparently by phasic or aphasic changes in sympathetic tone and finally (4) waves of even slower frequency and greater amplitude than the alpha waves, designated beta and gamma waves, the genesis of which is not understood.

The basic component of the plethysmogram, the volume pulse, normally exhibits a characteristic pattern. The apex is sharp and pointed; the systolic rise is more acute than the diastolic fall; the dicrotic notch is clearly discernible, located usually about the mid-portion of the diastolic limb and is relatively constant in position from beat to beat. Both contour and volume pulse amplitude remain relatively constant during any period of observation unless the subject is exposed to various stimuli.

This standard configuration is markedly altered by the presence of patent ductus arteriosus. (Fig. 3.) The changes consist of distinct blunting, broadening or flattening of the apex, loss in the normal slope difference of systolic ascent and diastolic descent, the limbs tending to become equal, and the dicrotic notch is found to vary in position with successive pulsations; usually it is located on the diastolic limb close to the apex, but on rare occasions it may be noted in a high anacrotic position. Finally, small but significant variations in general contour and amplitude are apparent from moment to moment. No significant alterations in respiratory, alpha, beta or gamma deflections have been found.

During the past eighteen months plethysmograms have been obtained in twenty-six patients clinically suspected of having

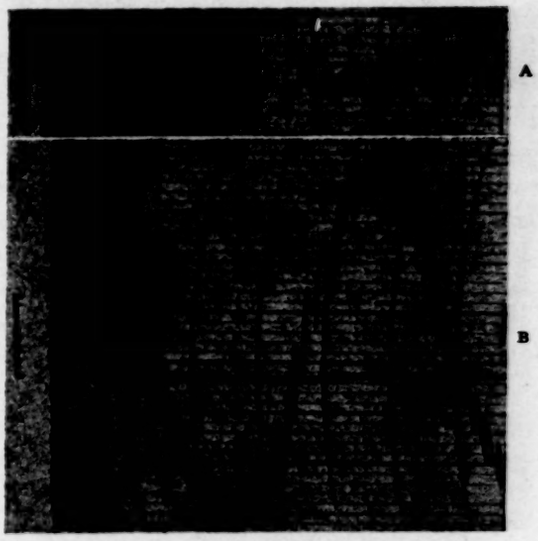


FIG. 2. Plethysmograms from a normal subject. A, from the second left finger; B, from the left great toe. Note that the respiratory fluctuations are well developed in the finger and indiscernible in toe, while the uncorrected volume pulse amplitude and alpha deflections are greater in the toe than in the finger.

patent ductus arteriosus. The essential clinical data are presented in Table I. A plethysmographic pattern considered typical of patent ductus was found in twenty-three subjects and a questionable or equivocal tracing in one.

In the following paragraphs the data obtained by means of plethysmography are compared with the observations made at operation and with those made by angiocardiography, electrocardiography, auscultation and sphygmomanometry.

Operative Findings. Seventeen patients were subjected to exploratory thoracotomy. One of these patients (J. O'C) had the tetralogy of Fallot and had undergone a

FIG. 3. A to C, plethysmograms from the finger in three instances of patent ductus arteriosus. Note the blunt apex, the absence of or barely discernible notch and the loss of slope variation with systole and diastole.

Blalock-Taussig operation at another hospital. The plethysmogram obtained three and one-half months after this procedure demonstrated the typical pattern of patent ductus. Of the remaining sixteen patients patent ductus was found in fifteen and patent interauricular septum in one. The plethysmogram in this latter case revealed no significant abnormalities. Characteristic plethysmograms were found in fourteen of the remaining fifteen patients. In the one instance in which a discrepancy existed between the plethysmographic and operative findings (the authors disagreed on interpretation) a relatively small ductus was found and ligated. Oxygen determinations of aortic and pulmonic arterial blood at the time of operation disclosed normal

TABLE I

ESSENTIAL CLINICAL AND LABORATORY FINDINGS IN TWENTY-SIX SUSPECTED INSTANCES OF PATENT DUCTUS ARTERIOSUS

Name	Age	BP	Murmur	ECG	Angiocardiogram	Plethysmogram	Operation	Diagnosis
P. P.	9	114/50	T	....	P	P	Lig.	P.D.
R. K.	31	122/82	T	N	P	P	Lig.	P.D.
E. deV.	8	110/70	N.T.	RVP	P	P	Lig.	P.D.
R. M.	7	80/40	T	N	E	P	Lig.	P.D.
M. F.	25	138/68	T	N	N.D.	P	Lig.	P.D.
J. L.	6	110/70	T	....	N.D.	P	Lig.	P.D.
C. A.	11	126/60	T	....	N.D.	P	Lig.	P.D.
C. O.	10	108/78	T	....	N.D.	P	Lig.	P.D.
M. K.	15	120/50	N.T.	....	N.D.	P	Lig.	P.D.
M. J.	3	120/76	T	N	N.D.	P	Lig.	P.D.
N. K.	4	104/68	T	....	N.D.	P	Lig.	P.D.
I. G.	6	110/60	T	....	N.D.	P	Lig.	P.D.
W. S.	28	100.60	N.T.	N	N.D.	P	Lig.	P.D.
M. K.	7	118/58	N.T.	N	N.D.	P	Lig.	P.D.
H. B.	6	90/40	T	....	P	P	N.D.	P.D.
B. U.	15	104/60	N.T.	N	P	P	N.D.	P.D.
C. K.	11	118/20	T	....	N.D.	P	N.D.	P.D.
T. C.	13	120/48	N.T.	N	N.D.	P	N.D.	P.D.
J. C.	4	90/26	T	N	N.D.	P	N.D.	P.D.
P. S.	32	124/68	T	N	E	P	N.D.	P.D.
M. H.	15	130/65	T	LAS	P	E	Lig.	P.D.
S. S.	21	126/46	N.T.	T in 1, 2, 3	P	P	N.D.	P.D.
S. B.	6	90/50	N.T.	RVP	P	P	....	Tetralogy of Fallot and patent ductus
J. O'C.	10	122/64	N.T.	RVP	N.D.	P	....	Post-Blalock operation
J. H.	2	108/64	N.T.	N	N.D.	N	....	Subaortic stenosis
B. M.	6	112/70	N.T.	High voltage	P	N	....	Interauricular septum

T—Machinery murmur
N.T.—Not typical
P—Positive
E—Equivocal
N.D.—Not done
P.D.—Patent ductus
Lig.—Ligation of patent ductus
N—Normal
RVP—Right ventricular preponderance
LAS—Left axis shift

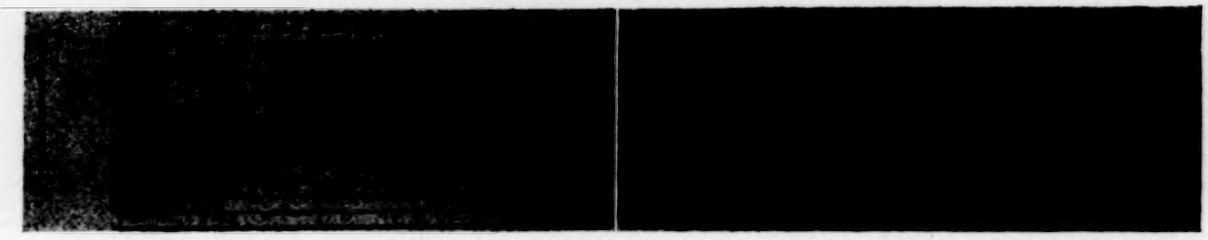
relationships. This may possibly indicate that physiologically insignificant amounts of blood were being shunted through the ductus, and may therefore serve to explain the difficulty in interpreting the plethysmographic changes in this patient.

Angiocardiography. Angiocardiography has proven of inestimable value in diagnosis of various forms of congenital heart disease. A characteristic angiocardiogram has been described in cases of patent ductus.[1] Angiocardiograms were obtained in eleven patients and a characteristic infundibulum was demonstrable in nine. In the remaining two the findings were considered suggestive. In this same series a diagnostically significant plethysmogram was found in nine patients. The two patients with a negative or doubtful plethysmogram had positive angiocardiograms. They were subjected to exploratory thoracotomy and, as mentioned previously, an interauricular septal defect was found in one and a relatively small ductus in the other. In the two patients with suggestive angiocardiograms, plethysmograms considered typical of patent ductus were obtained. One of these two patients was operated upon and a patent ductus found and ligated.

Electrocardiography. It is well known that the electrocardiographic pattern is usually normal in patients with patent ductus. The presence of right or left ventricular preponderance either speaks against diagnosis of patent ductus or indicates coexistence of other cardiac defects.[4,8] In general, our experiences confirm these observations. Of seventeen patients in whom electrocardiograms were available for analysis the tracings were normal in eleven. Typical plethysmograms were obtained in ten of these eleven patients. The exception revealed an anacrotic notch and systolic plateau on the pressure pulse tracing, slight left ventricular enlargement on fluoroscopy and a loud systolic murmur over the upper portion of the sternum on phonocardiography. Subaortic stenosis was considered the most likely diagnosis. Abnormal electrocardiograms were found in the remaining six patients. There were three instances of right ventricular preponderance, two in patients with the tetralogy of Fallot. One of these, previously described, had undergone the Blalock procedure. In the other the existence of concomitant patent ductus was entirely unsuspected until demonstrated by the plethysmogram and subsequently by the angiocardiogram. There was one patient, found to have an interauricular septal defect, in whom the electrocardiogram revealed high voltage QRS complexes in the limb leads. The plethysmogram was normal in this individual. One electrocardiogram revealed a left axis shift; this was found in the patient described previously in whom the plethysmogram was questionable and in whom operation disclosed a small ductus. The last patient in this series revealed striking electrocardiographic abnormalities characterized by tall notched P waves, QRS complexes of high voltage and inversion of the T waves in the standard leads. The pulse pressure was high. The phonocardiogram indicated the existence of a loud systolic murmur over the entire precordium with a faint diastolic component limited to the pulmonic area. The plethysmogram was characteristic of patent ductus and the angiocardiogram presented no abnormalities other than the characteristic infundibulum.

Blood Pressure. The influence of patent ductus on systemic arterial pressure is fairly well shown in our series. In fifteen cases there was a pronounced and in two cases a slight increase in pulse pressure produced primarily by a low diastolic level. Systolic and diastolic pressures were well within the normal range in the remaining seven patients. Typical plethysmograms were obtained in this latter group and operation subsequently disclosed a patent ductus in each instance.

Murmurs. The classical machinery murmur was present in fifteen of the twenty-six patients. Of the eleven in whom the murmur was absent, two were found to have a harsh, rough precordial systolic murmur associated with a faint (grade II) diastolic



A B

FIG. 4. A and B, plethysmograms from the same finger before and after ligation of a patent ductus. Note that in the postoperative tracing the apex is sharp and the dicrotic notch is quite distinct.

murmur over the pulmonic area. A systolic murmur of grade III and IV intensity, maximal over the second left interspace, was audible in two patients. In two instances, both with tetralogy of Fallot, exact significance of the auscultatory findings could not be properly evaluated. In the remaining five, systolic murmurs of varying intensity, usually of grade IV, were found over different parts of the precordium. Thus nine of the twenty-four patients in whom a diagnosis of patent ductus was substantiated either by operation or additional diagnostic criteria failed to present the machinery murmur. Plethysmography indicated the nature of the defect in eight of this group and gave uncertain results in the ninth patient.

Plethysmogram Following Closure of Patent Ductus. In our series sixteen patients were subjected to exploratory thoracotomy for closure of a suspected ductus. In fifteen a patent ductus was found and ligated. In the remaining instance, described previously, a patent interauricular septum was found. Plethysmograms were obtained in all fifteen patients seven to fourteen days postoperatively; in eleven the tracings had become normal as judged by the appearance of a sharper apex, and a distinct dicrotic notch constant in position. (Fig. 4.) Fluctuations in contour and volume amplitude tended to disappear, and the difference in the slope of the systolic and diastolic limbs became more pronounced. One patient examined two weeks after operation failed to disclose any significant plethysmographic alteration; reexamination a year later revealed an entirely normal tracing. In the three remaining patients, plethysmograms obtained within two weeks after operation were substantially the same as the preoperative records although in each, closure of the ductus had been accomplished successfully as was shown by the disappearance of the characteristic murmur and by a decrease in the pulse pressure. Apparently the plethysmogram does not become normal immediately after operation in all cases. This seems to be in agreement with the well known postoperative persistence of a pulmonic systolic murmur of varying intensity, and of the characteristic infundibulum on the angiocardiogram. Such findings may serve to indicate the continued presence of certain vascular alterations which may account for the continued postoperative presence of an abnormal plethysmographic pattern.

COMMENTS

As yet the circulatory factors underlying production of the characteristic plethysmographic pattern in patent ductus arteriosus are not clearly understood. An increase in pulse pressure plays no significant rôle. This is indicated by the observation that in three instances of aortic insufficiency, two of syphilitic and one of rheumatic origin, a similar volume contour was not obtained. However, during the course of these investigations we have observed the typical blunting and flattening of the volume pulse in lesions other than patent ductus. These included two cases of arteriovenous and one case of arteriosclerotic aortic aneurysm. (Fig. 5.) The similarity of the tracings in patent ductus and arteriovenous aneurysm is readily understood. The identity of the pattern in the presence of a

large arterial aneurysm and in patent ductus may be explained on the assumption that both the shunt and the arterial sac, functioning as a surge tank, smooth out comparatively small, fast volume and pressure changes such as the dicrotic notch. The mechanism may be compared to that of an electromechanical equivalent of a by-pass condenser. This explanation would also account for the equiphasic systolic and diastolic limbs and the flattening of the apex. Changes in volume amplitude from moment to moment are accounted for by fluctuations in volume flow to the periphery induced by a variable diversion of blood through the shunt with each systole of the heart. A large arterial aneurysm behaving as a resevoir may produce similar fluctuations in the circulating blood volume per beat.

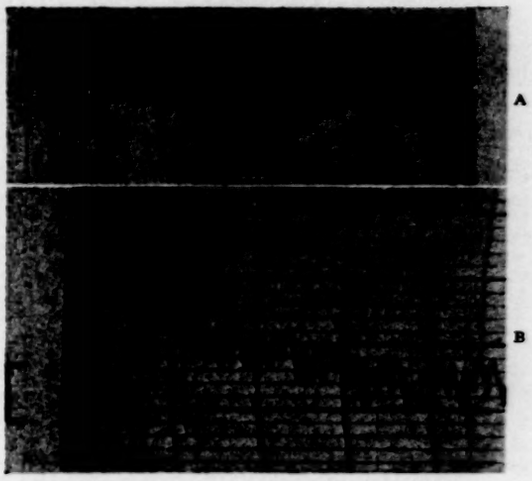


FIG. 5. A, plethysmogram from the great toe of a patient with an arteriovenous aneurysm. B, plethysmogram from the great toe of a patient with an arteriosclerotic aortic aneurysm. Note the similarity of these tracings and those noted in instances of patent ductus.

A B

FIG. 6. Plethysmograms from the finger of a normal subject before and after the administration of 1/100 gr. nitroglycerin. A, the control. Note the marked increase in volume pulse amplitude and the sharp decline in the position of the dicrotic notch following nitroglycerin.

Absence of similar plethysmographic alterations in the presence of free aortic insufficiency and in various intracardiac shunts is attributable to the fact that the major volume changes occur centrally within the chambers of the heart.

COARCTATION OF THE AORTA

The finger and toe plethysmograms normally differ. Although the two are essentially similar in contour, in the position of the dicrotic notch and in the slope of the component limbs, the amplitude of certain intrinsic volume deflections may differ sharply under normal conditions. Thus the uncorrected volume pulse and alpha waves are much larger in the great toe than in the finger. The reverse is true of the respiratory waves. (Fig. 2.)

We have also observed that the sublingual administration of nitroglycerin produces characteristic alterations in the normal plethysmogram. These consist of a distinct increase in volume pulse amplitude, of a moderate increase in the amplitude of the alpha waves and in a pronounced descent in the position of the dicrotic notch on the diastolic limb. (Fig. 6.) Increases in amplitude are proportional in the finger and toe.

These variations in the normal and in the normal postnitroglycerin plethysmograms are diagnostically altered in the presence of coarctation of the aorta. When this condition is present, the amplitude of both the

A B

FIG. 7. Plethysmograms in a patient with coarctation of the aorta. A, tracings from the finger; B, tracing from the great toe. Note the pronounced reversal in volume amplitude relationships.

uncorrected volume pulse and the alpha waves in the toe never exceeds that in the finger. If the aorta is markedly constricted, the normal volume relationship may be reversed. (Fig. 7.) Thus the tracing from the toe may reveal a volume pulse of markedly diminished amplitude and an absence of alpha waves while the record from the fingertip shows well developed volume pulse deflections and alpha waves of large amplitude. Furthermore, the characteristic nitroglycerin effect may be manifest in the finger tracing while insignificant alterations appear in the toetip plethysmogram.

We have had the opportunity of analyzing the plethysmograms of six patients with suspected coarctation of the aorta because of diminished or absent femoral pulsations, or suggestive cardiac murmurs or radial pulse waves preceding the femoral pulse waves. Roentgen examination failed to reveal the characteristic notching of the ribs in any of these persons. Only two of the six patients presented classical hypertension in the upper and hypotension in the lower extremities. In three patients arterial pressure levels were similar in the upper and lower extremities; in the remaining patient normal pressure relationships existed. Angiocardiograms were obtained in five of these six patients and the clinical impression was confirmed in each instance.

A plethysmographic diagnosis of coarctation was made in all patients either because of a reversal in volume relationships in the tracings obtained from the finger and toe, or the aforementioned variation in the response to nitroglycerin or the fact that the uncorrected volume pulse amplitude and alpha waves in the toe did not exceed those in the finger. In general, the plethysmogram, angiocardiograms and the additional clinical findings were comparable. When a pronounced degree of coarctation was demonstrated in the angiocardiogram, the plethysmogram showed pronounced reversal in volume relationships. This is exemplified in Figure 7 and was obtained in one of the patients who had hypertension in the upper extremities.

The angiocardiogram and the plethysmogram yield complementary rather than identical information. This is evidenced by the findings in two of the six patients in whom a significant degree of coarctation was demonstrable on the angiocardiograms. The plethysmograms, however, revealed volume pulse amplitudes in the toe either equal to or slightly smaller than those obtained from the finger. Such instances presumably indicate the existence of a fairly adequate collateral circulation. Thus the correlation of angiocardiographic and plethysmographic findings can be expected to aid in defining the indications for surgical treatment in cases of coarctation.

Application of microplethysmography to clinical medicine is as yet in its infancy. The technic offers a fruitful field for investigation, and it is as much the purpose of this report to encourage investigations by other groups as to present our own results. We

have used the microplethysmograph in various other disorders of the cardiovascular system and additional results are soon to be published. Our investigations in the problem of congenital heart disease are continuing.

We believe we are justified in stating that the microplethysmogram has been a valuable aid in diagnosis of patent ductus arteriosus and coarctation of the aorta. It should be part of the preoperative diagnostic survey, as much as physical examination and electrocardiography. Ease of recording and interpretation make the method especially valuable in those patients in whom typical signs are not present, or in whom such factors as age, sensitivity to diodrast or absence of necessary equipment make angiocardiography and cardiac catheterization inadvisable or impossible.

SUMMARY AND CONCLUSIONS

1. Microplethysmography has been applied to the study of congenital heart disease. Present investigations have dealt with patent ductus arteriosus and coarctation of the aorta.

2. Tracings of the finger and toetip volume pulsations were recorded and characteristic patterns were found.

3. In patent ductus the following alterations were found: the apex of each wave was blunt, broad, or flat; there was a loss of the normal difference between systolic rise and diastolic fall, the limbs tending to be equal; the dicrotic notch was either absent or barely discernible and tended to vary in position from beat to beat; small but significant fluctuations in contour and volume amplitude appeared from moment to moment.

4. In coarctation of the aorta normal volume relationships in the finger and toe tracings were lost so that the volume amplitude and alpha waves in the fingertip tracing were greater than or at least equal to the analogous waves in the tracing from the toetip.

5. The findings illustrate the value of microplethysmography in diagnosis of these anomalies.

REFERENCES

1. Sussman, M. L. and Grishman, A. A discussion of angiocardiography and angiography. *Adv. Int. Med.*, 2: 102, 1947.
2. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C. and Evans, J. M. Studies of congenital heart disease. III. Venous catheterization as a diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect and auricular septal defect. *J. Clin. Investigation*, 26: 561, 1947.
3. Geiger, A. J., Anderson, H. C., Winkler, A. W. and Kaplan, H. S. Cardiovascular catheterization as an aid in diagnosis of abnormal cardiovascular communications. *Connecticut M. J.*, 10: 895, 1946.
4. Levine, S. A. and Geremia, A. E. Clinical features of patent ductus arteriosus with special reference to cardiac murmur. *Am. J. M. Sc.*, 213: 385, 1947.
5. Neumann, C., Cohn, A. E. and Burch, G. E. A study of the influence of the character of an examining room on the peripheral blood vessels of normal, hypertensive and senile subjects. *J. Clin. Investigation*, 21: 651, 1942.
6. Burch, G. E. A new sensitive portable plethysmograph. *Am. Heart J.*, 33: 48, 1947.
7. Burch, G. E., Cohn, A. E. and Neumann, C. A study by quantitative methods of the spontaneous variation in volume of the finger tip, toe tip and posterior-superior portion of the pinna of resting normal white adults. *Am. J. Physiol.*, 136: 433, 1942.
8. Barnes, A. R. and Harrington, S. W. The surgical treatment of patent ductus arteriosus. *Mod. Con. Cardiovascular Dis.*, 14: 2, 1945.

Pheochromocytoma*

Report of a Case, with a New Diagnostic Test

VICTOR GUARNERI, M.D. *and* JAMES A. EVANS, M.D.

Boston, Massachusetts

THE first successful excision of a pheochromocytoma was reported by C. H. Mayo[15] in 1927. Since then, there has been an increasing number of reports dealing with removal of this tumor. MacKeith,[14] in an excellent review of the subject in 1944, stated that 165 cases of pheochromocytoma had been reported. Of these, thirty-six patients were operated on with ten fatalities. Since 1941, twenty-nine additional cases have been reported in English and American literature.[2–6,8–14,16–20,22,24–26] Eighteen patients underwent operation and two deaths occurred.[18,25] It is the purpose of this paper to describe an additional case of chromaffinoma of the adrenal gland, diagnosed preoperatively and successfully removed, in which a new diagnostic test was employed.

CASE REPORT

A twenty-three year old white, unmarried woman was first seen at the Clinic in February, 1946 complaining of attacks of weak spells. Cholecystectomy, appendectomy and dental extraction had been performed to relieve her present complaints but without avail. The patient stated that she had been in fairly good health until three years before admission when she noted onset of five or six daily attacks of weakness which would last five to ten minutes. These attacks came on suddenly without warning and at times awakened her from a sound sleep. The attacks were described by the patients as follows: "Suddenly there occurs a feeling that all the blood is draining out of my body, and I feel weak. There is an aching in my legs and a burning sensation in the pit of my stomach. Then I get a pain in my chest which goes down my arms, shortness of breath, and palpitation of the heart. Next there is dizziness and a ringing in the ears followed by a severe throbbing headache and a pain in the back of the neck. Cold sweat breaks out in my hands and face and the hands become cold and blotchy while the scars on my body become purple. Then nausea and vomiting follow and the attack ceases but leaves me woozy and weak." Most of the attacks occurred after meals. Between attacks she felt perfectly well. Elsewhere she had been treated with a course of histamine by intravenous drip. It is interesting to note that in spite of the fact that histamine reproduced the symptoms the diagnosis was overlooked.

The patient was well nourished but poorly developed. The general system review for other symptoms was negative. Skull, pupillary reactions and ocular muscles were normal. Ophthalmoscopic examination revealed normal fundi. Lungs and heart were normal; apical and radial rates were 100 with regular rhythm. Blood pressure in the right arm was 102 mm. systolic and 94 mm. diastolic, in the left arm 106 mm. systolic and 84 mm. diastolic. No other physical findings pertinent to her present illness were discovered.

Tests of the urine were negative except for a trace of albumin. Hemoglobin was 13.6 Gm., red cell count 5,050,000 and white cell count 11,350. The differential count revealed 80 per cent polymorphonuclear cells and 20 per cent lymphocytes. Sedimentation rate was 22 mm. per hour; the Hinton test was negative. The fasting blood sugar was 100 mg. per 100 cc. During separate attacks of weakness the blood sugar was 147, 156 and 166 mg. per 100 cc., respectively. Serum calcium determination was 9.8 mg. per 100 cc., serum phosphorus 3.4 mg. per 100 cc., alkaline serum phosphatase 5.0 Bodansky units, acid phosphatase 0.4 units. Serum potassium during an attack was 21.3 mg. per 100 cc. (normal 18 to 22 mg. per 100 cc.).

* From The Department of Internal Medicine, The Lahey Clinic, Boston, Mass.

Gastric analysis showed free hydrochloric acid of 10 and total acid of 30. Basal metabolic rate was 9 per cent before and +36 per cent during an induced attack.

An electrocardiogram before an induced attack showed a rate of 100, high P_2 and flat T_3. During an induced attack the rate was 120 and T_3 became inverted. An electro-encephalogram was interpreted by Dr. Milton Greenblatt as showing a definitely atypical record consistent with a mild form of epileptic dysrhythmia, with no localized abnormality.

Roentgenologic examination after a barium enema showed the splenic flexure high under an elevated left diaphragm. Roentgenogram of the skull showed no localized changes and a normal sella turcica. Intravenous pyelography revealed the left kidney to be flattened superiorly so that the major superior calyx was at right angles to the pelvis. The depressed left kidney and elevated left diaphragm were considered to be consistent with a space-filling lesion in the left upper quadrant.

While the patient was at rest in the hospital, blood pressure ranged between 80 and 110 mm. systolic and 60 to 80 mm. diastolic. The patient had many spontaneous attacks, during one of which the blood pressure level rose as high as 230 mm. systolic and 140 mm. diastolic. We were able to induce attacks with 0.5 mg. of histamine intravenously and 25 mg. of mecholyl subcutaneously. With histamine, blood pressure rose from 80 to 185 mm. systolic and from 62 to 130 mm. diastolic; with mecholyl, from 104 to 210 mm. systolic and from 80 to 140 mm. diastolic (Fig. 1). The spontaneous attacks lasted from five to ten minutes. We were not able to induce attacks by abdominal massage, hyperventilation, epinephrine, nitroglycerine, changes in position or by the cold pressor test.

Operation was performed on the twenty-fifth hospital day by Dr. Richard B. Cattell. She

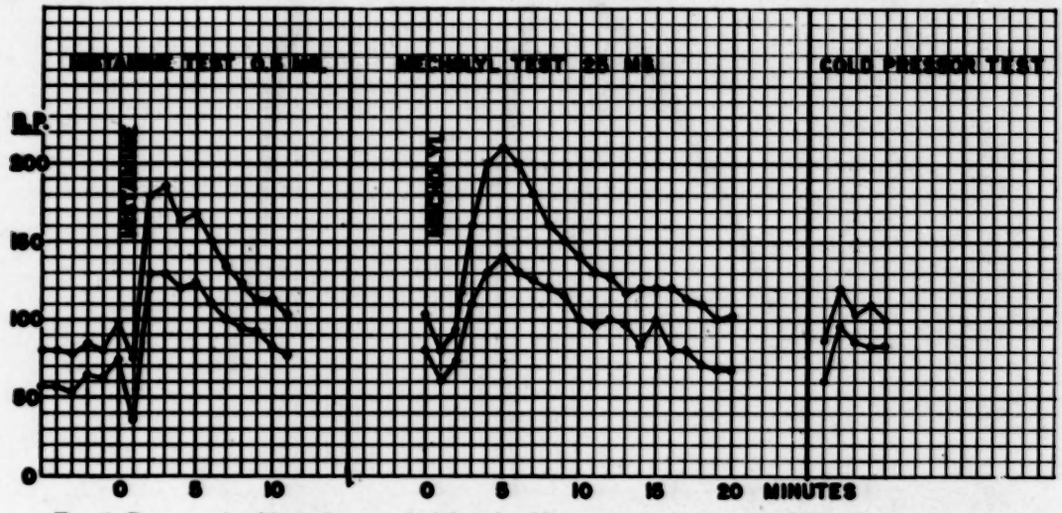


FIG. 1. Preoperative histamine, mecholyl and cold pressor tests in a case of pheochromocytoma.

was prepared as follows: 10 mg. of desoxycorticosterone acetate was administered intramuscularly daily for five days before operation. Adrenocortical extract, 25 cc. intramuscularly and 25 cc. in 1,000 cc. of 5 per cent glucose and physiologic saline solution, was given the night before and immediately before operation. Whole blood, 500 cc., was also given during the surgical procedure.

At operation the right adrenal gland was explored first and found to be normal. During exploration blood pressure rose to 190 mm. systolic and 132 mm. diastolic. Through a left lumbar incision the tumor mass was readily exposed but it was necessary to resect a portion of the twelfth rib in order to remove the tumor mass. In doing so the pleura was accidentally nicked and respiratory distress developed. This was remedied by closing the tear after decompression of the pleural cavity and expansion of the lung by positive pressure. The tumor was found to be above and compressing the superior pole of the kidney but was not adherent to it. During manipulation of the tumor the blood pressure rose to 260 mm. systolic and 185 mm. diastolic and just before the pedicle was clamped pulmonary edema developed. The blood pressure was unobtainable. In retrospect, this was thought to be caused by extreme vasoconstriction with conse-

quent left ventricular failure accompanied by pulmonary edema, all of which led to a precipitate drop in blood pressure as measured in the brachial artery. The pedicle was immediately clamped and a transfusion of whole blood was started. Epinephrine, 0.5 cc., was given intramuscularly and 0.2 cc. intravenously. The blood pressure remained unobtainable for one-half hour after which it rose to 80 mm. systolic and 40 mm. diastolic. The tumor was quickly removed, one-half the left adrenal gland was left intact and the incision was closed. The patient was given oxygen by mask until most of the signs of pulmonary edema disappeared. She was then returned to her room; the blood pressure was 80 mm. systolic and 40 mm. diastolic. The anesthesia used was ether, later supplemented by cyclopropane.

Postoperatively, the patient had a relatively uneventful course except for the development of patchy atelectasis at the base of the left lung and a low grade temperature for several days. This was treated with penicillin. The postoperative blood pressure ranged from 84 to 126 mm. systolic and from 30 to 98 mm. diastolic, becoming stabilized to normal levels on the second postoperative day. Intravenous fluids were also administered routinely after operation. She was discharged on the seventeenth postoperative day. The mecholyl test repeated prior to discharge was normal; however, there was still a hyper-reactive response to histamine, 0.5 mg. intravenously. (Fig. 2.)

When seen again two months after discharge, the patient felt perfectly well, had gained some weight and had had no further attacks since operation. The blood pressure at this time was 110 mm. systolic and 70 mm. diastolic when she was lying down, 100 systolic and 70 diastolic sitting and 80 systolic and 70 diastolic when standing. Albumin had disappeared from the urine.

On pathologic examination by Dr. Shields Warren, the specimen was found to be an encapsulated mass, 8 cm. in diameter, weighing 260 Gm. The mass had a smooth, glistening capsule with injected vessels running over the surface. The cut surface showed practically the entire mass to be occupied by a soft, bright red, jelly-like material, except for an irregular, yellow, encompassing border. Microscopically, none of the architecture of the adrenal gland remained. The entire mass was composed of cells which were apposed to each other in clusters and separated by fine strands of connective tissue in which numerous capillaries coursed. These clusters formed broad sheets punctuated by arterioles and dilated, congested vessels. The individual cells varied in size from about 15 to 45 μ, averaging about 25 μ; they were sometimes oval or round but more often polygonal. The cytoplasm was acidophilic, slightly granular and contained vacuoles. The nuclei were oval, occasionally round, vesicular and measured about 10 to 20 μ in diameter; they were centrally or slightly eccentrically placed; rare nuclei were hyperchromatic but there were no mitoses and no multinucleated cells. Some portions of the tumor were covered by a thick capsule and there was invasion into this fibrous covering. Microscopic diagnosis was pheochromocytoma.

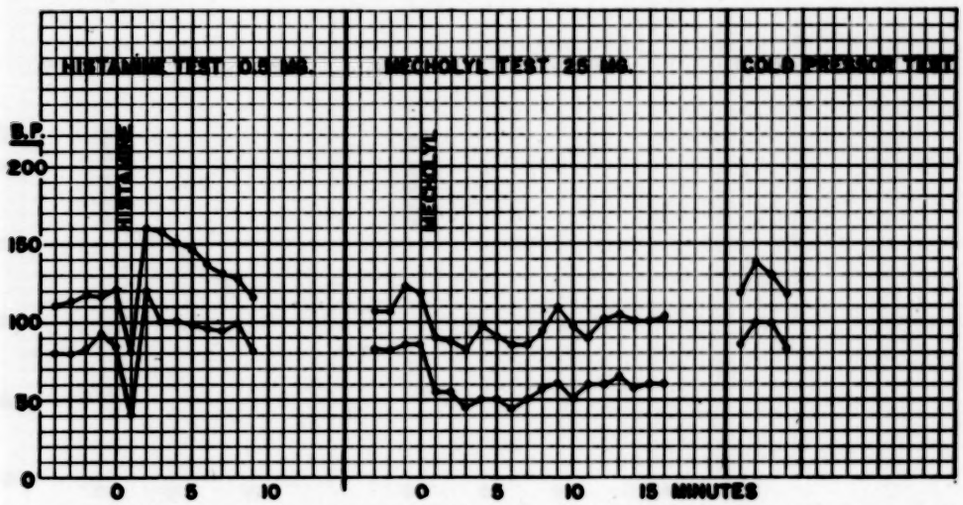


FIG. 2. Postoperative histamine, mecholyl and cold pressor tests in a case of pheochromocytoma. Note that the patient still reacts to histamine (hyper-reactor) but does not react to mecholyl after operation.

COMMENTS

Symptomatology, pathology and other general features of chromaffin tumors have been discussed elsewhere[14,23] and need not be repeated. Our remarks will be confined to a description of the effects of certain drugs on a patient with pheochromocytoma. These observations have been utilized to construct a diagnostic test for the presence of this tumor.

The high surgical mortality rate of 28 per cent reported by MacKeith[14] has generally been attributed to the shock effect of sudden withdrawal of epinephrine following excessive rise of blood pressure during the operation resulting from manipulation of the chromaffin tumor. It occurred to Dr. Elmer C. Bartels, of our medical staff, that an excess of anti-epinephrine factor (acetylcholine), predominant after removal of the tumor, might be responsible for the shock so often experienced immediately after excision of the tumor. He suggested, therefore, that mecholyl be given our patient preoperatively, reasoning that if an excess of acetylcholine was present, the patient should show none of the usual depressive effects from what would be to her a comparatively small addition of acetylcholine. Mecholyl (acetyl β methylcholine), 25 mg., therefore, was administered subcutaneously. The patient, however, exhibited the usual fall in blood pressure and then, to our surprise, within two minutes the blood pressure rose to 210 mm. systolic and 140 mm. diastolic. (Fig. 1.) A smaller dose of mecholyl (15 mg.) produced a similar response as did administration of an additional 10 mg. at the peak of the blood pressure elevation following the 15 mg. dose. It was apparent from these observations that there was no anti-epinephrine protection from excess acetylcholine and furthermore that mecholyl could not be used during the operation to protect the patient from paroxysmal hypertension during manipulation of the tumor. It could be reasoned also that atropine, the antidote for acetylcholine, could not be used to protect the patient from the partial collapse of blood pressure that usually occurs immediately after removal of a chromaffin tumor.

In order to determine the reason for this unusual response to mecholyl the patient was given atropine before administration of this substance. (Fig. 3.) Atropine has no

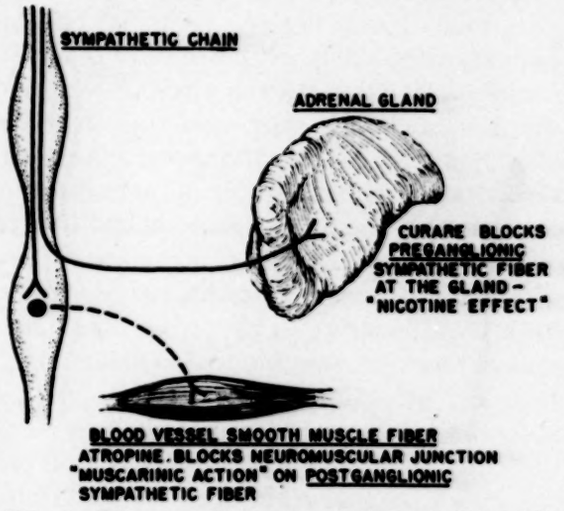

SYMPATHETIC CHAIN
ADRENAL GLAND
CURARE BLOCKS PREGANGLIONIC SYMPATHETIC FIBER AT THE GLAND - "NICOTINE EFFECT"
BLOOD VESSEL SMOOTH MUSCLE FIBER
ATROPINE BLOCKS NEUROMUSCULAR JUNCTION "MUSCARINIC ACTION" ON POSTGANGLIONIC SYMPATHETIC FIBER

FIG. 3. Diagrammatic representation of "nicotinic effect" and "muscarinic action."

effect on autonomic ganglia.[7] Its action is limited to blockage of the "muscarinic" or peripheral effects of parasympathetic activity, the postganglionic response. If the mecholyl response were a manifestation of muscarinic activity only, it should be blocked by atropine. If it were due to ganglionic stimulation, atropine should have no effect. Atropine, 1/75 gr., was given subcutaneously after the resting blood pressure became stabilized. Five minutes later 25 mg. of mecholyl was given subcutaneously. No initial fall in blood pressure was observed, but within two minutes the blood pressure had risen to 230 mm. systolic and 190 mm. diastolic as in the original experiment without atropine. The various muscarinic side reactions of mecholyl, however, failed to occur. Approximately three hours later another 25 mg. of mecholyl was given. This time a slight fall of 10 mm. of mercury in pressure was recorded followed by a prompt rise. Again, none of the side reactions of mecholyl were present. These results would seem to indicate that the hypertensive effect of mecholyl in this patient was not the result of any peripheral

muscarinic action since the manifestations of such action, including the initial fall in blood pressure presumably due to vasodilatation, could be blocked by atropine.

The adrenal gland is innervated by preganglionic cholinergic fibers and is functionally equivalent to an autonomic ganglion. Theoretically, mecholyl could have elevated the blood pressure by a direct stimulating action on the synapse between the preganglionic fiber and the adrenal gland and its tumor. If this were true, it should have been possible to prevent the response by use of a drug which blocks transmission of impulses across the preganglionic synapse. Nicotine would have been the ideal drug to use for this purpose; unfortunately it was not readily available. Instead, we used curare, which is an autonomic inhibitor[7] less potent, however, than nicotine.[14] The patient was given 5 cc. of curare (intocostrin) intravenously. Within a few minutes, muscle and respiratory paralysis developed. While respiration was being maintained by positive pressure oxygen administration, 25 mg. of mecholyl was given subcutaneously. The typical mecholyl response occurred, first an initial fall in blood pressure followed by a rise in two minutes to 218 mm. systolic and 132 mm. diastolic. Inhibition of the preganglionic synapse failed to prevent the mecholyl-induced hypertension, suggesting either that mecholyl does not directly stimulate the synapse or that curare failed to block transmission across the synapse.

Mecholyl (acetyl β methylcholine), in contradistinction to acetylcholine, has principally a muscarinic action.[7] It also has a nicotinic or ganglionic action[7] but this is minimal. In atropinized animals it is usually impossible to produce elevation of blood pressure with mecholyl.[7] In normal human beings response to mecholyl is a fall in the blood pressure level. The mechanism of mecholyl hypertension in pheochromocytoma is not entirely clear. Several possibilities exist: (1) The preliminary fall in blood pressure due to vasodilatation may act as a stimulus to compensatory sympathetic activity. In the presence of a chromaffin tumor, a large reservoir of sympathomimetic substance, there may be an exaggeration of the compensatory response with resultant hypertension. Since response could be elicited in spite of elimination of the hypotensive stage by atropine, however, this explanation would appear invalid. (2) The ganglionic (nicotinic) action of mecholyl, even though slight, may be sufficient to produce hypertension when the effector structure is as potent as is pheochromocytoma. Militating against this is the fact that curare failed to block the mecholyl response. It is difficult to determine whether or not the dose of curare was sufficient to block completely the preganglionic synapse. (3) Since the curare effect was potent enough to suspend respiration, it would seem likely that the dose would have been enough to paralyze the preganglionic sympathetic-adrenal synapse. If this were true, then the hypertensive response to mecholyl in this patient could have been the result of the direct action of mecholyl on the chromaffin tumor itself. This appears to us the most probable interpretation.

Roth and Kvale[22] administered 1 to 2 mg. of mecholyl by intravenous drip over a fifteen-minute period to a patient with a pheochromocytoma and failed to reproduce the typical paroxysmal hypertension. In view of our findings we believe that the method of administration was too slow and the dose too small to elicit response. The unique hypertensive response produced by mecholyl in our patient with a pheochromocytoma suggests use of the drug as a diagnostic test.

MECHOLYL TEST

The mecholyl test consists of administration of 25 mg. of the drug subcutaneously following a period of rest to obtain stabilized blood pressure and pulse rate. The blood pressure and pulse rate are recorded, after mecholyl is given, at one-minute intervals until they return to normal in fifteen to thirty minutes. A positive test is shown by a marked rise in the systolic and diastolic pressures. In this case there was a rise of

106 mm. systolic and 60 mm. diastolic above the resting levels following a preliminary fall lasting about one minute. The pressure returned to normal in fifteen minutes. Associated with the rise in blood pressure were all the symptoms characteristic of a paroxysmal attack of hypertension due to pheochromocytoma. In addition, the patient experienced the side reactions of mecholyl, which include nausea, salivation, epiphora, sweating and dyspnea.

In order to obtain information regarding the specificity of the test, it was performed on twenty-seven additional patients, ages twenty to sixty. Seven were normal and twenty had hypertensive vascular disease. Of the latter group eighteen had essential hypertension. Two had chronic glomerulonephritis with hypertension. In twenty-two the cold pressor test was also done and in nine the histamine test, described by Roth and Kvale,[21,22] was performed.

The results in these twenty-seven controls were as follows: (1) With one exception, the twenty-seven patients showed an identical response to mecholyl; an immediate initial fall of systolic and diastolic pressures followed by a gradual return to normal levels in fifteen to thirty minutes. Almost all of the patients experienced sweating, salivation, tearing, dyspnea, flushing and a sensation of warmth, nausea, urge to defecate or urinate and an occasional headache. These subsided with return of the blood pressure to normal. In two hypertensive individuals the test had to be terminated with atropine at the end of ten minutes. One who complained of fainting spells developed a convulsive seizure associated with a marked fall in blood pressure; the other complained of severe substernal pain during the test. In one patient the systolic blood pressure rose 6 mm. of mercury over normal without a preliminary fall. The diastolic pressure, however, fell initially and never rose above the resting level. (2) Of the twenty-two patients on whom the cold pressor test was performed, seventeen showed a normal response consisting of a transient slight elevation of blood pressure less than 20 mm. Five showed a rise of more than 20 mm. and may be considered as hyper-reactors. These five, however, had perfectly normal mecholyl tests. (3) Of the group of nine patients on whom the histamine test was done, five had a rise in blood pressure of 20 mm. or more and are considered as hyper-reactors to histamine. Results of this

TABLE I

VARIATIONS IN BLOOD PRESSURE FOR VARIOUS TESTS*

Case	Histamine Test				Mecholyl Test				Cold Pressor Test			
	Blood Pressure		Difference in Pressure		Blood Pressure		Difference in Pressure		Blood Pressure		Difference in Pressure	
	At Rest	During Test	Systolic	Diastolic	At Rest	During Test	Systolic	Diastolic	At Rest	During Test	Systolic	Diastolic
21	154/96	180/110	+26	+14	156/80	116/20	−40	−60	156/90	158/96	+2	+6
26	158/106	192/98	+34	−8	124/86	130/40	+6	−46	122/84	126/90	+4	+6
19	124/74	156/100	+32	+26	126/76	124/40	−2	−36	130/74	136/90	+6	+16
22†	130/80	188/140	+58	+60	116/76	100/60	−16	−16	124/78	130/92	+6	+14
27	120/70	164/84	+44	+14	130/78	80/48	−50	−30	140/76	166/90	+26	+14
		166/80	+46	+10								

* Tests were performed on five patients considered to be histamine hyper-reactors, two hypertensives and three normotensives. Note the rise in both systolic and diastolic pressures is greater after histamine than during cold pressor test in both hypertensive and normotensive subjects.

† Received 0.5 mg. of histamine instead of 0.05 mg.

group are shown in Table 1. These five patients had normal mecholyl tests. Figure 4 shows graphically a typical mecholyl response in one of these patients. One patient in the histamine group in whom a diagnosis was made of "anxiety state," was given 0.5 mg. of histamine instead of 0.05 mg. He showed a fall in blood pressure from 130 to 60 mm. systolic and from 80 to 0 mm. diastolic, followed by a prompt rise to 188 mm. systolic and 140 mm. diastolic, with a return to normal in forty-five minutes. This would appear to be a positive histamine test for pheochromocytoma. In view of the absence of other findings suggestive of pheochromocytoma, however, surgical exploration was not deemed justified. Both the mecholyl and cold pressor tests were normal. The cause for the rise in blood pressure in this patient is not definitely known. Unfortunately the test was not repeated using the usual 0.05 mg. dose of histamine.

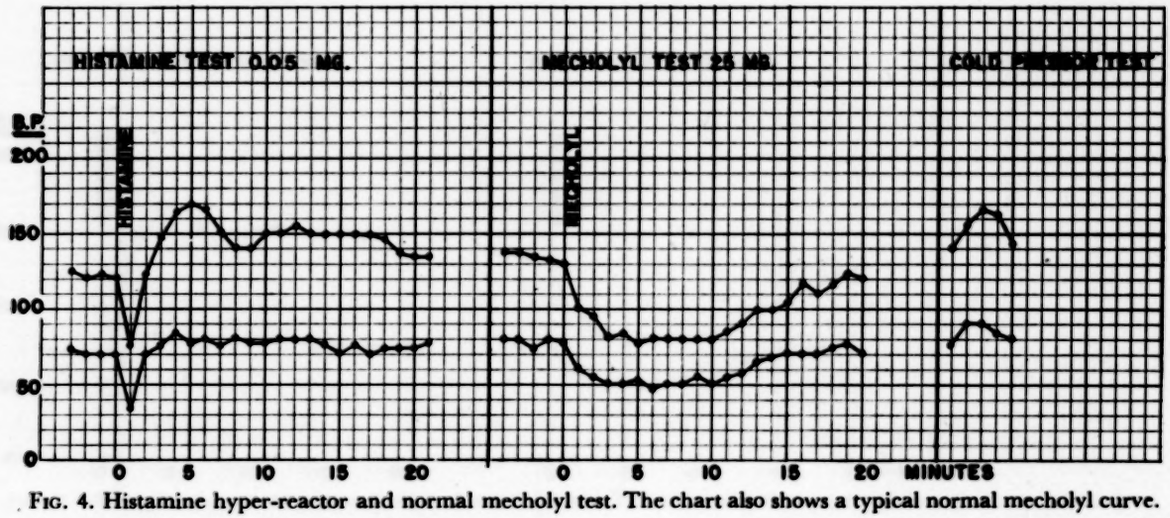


FIG. 4. Histamine hyper-reactor and normal mecholyl test. The chart also shows a typical normal mecholyl curve.

Roth and Kvale reported that their patients had a smaller rise of blood pressure to histamine than to the cold pressor test. We found that four histamine reactors (two of these were hypertensive, two normotensive) did the opposite (Table 1), that is, when the same dose of histamine was given as Roth and Kvale used, the blood pressure level rose an average of 34 mm. systolic and 11.5 mm. diastolic. One of these four patients had the significant rise of 46 mm. systolic and 14 mm. diastolic. The mecholyl test in this patient showed no rise of blood pressure after the usual fall and there were no symptoms suggestive of paroxysmal hypertension. In these four patients, especially the last one described, there appears to be a suggestive test for pheochromocytoma although not the striking rise of 100 mm. systolic described in pheochromocytoma by Roth and Kvale. Since in no case except the patient with the pheochromocytoma did mecholyl produce a rise in both systolic and diastolic pressures, we suggest that the mecholyl test may be more specific than the histamine test in diagnosis of this type of neoplasm. We realize that definite conclusions cannot be drawn from so limited experience as is described here. Nevertheless, the results suggest the need for further trial of mecholyl as an aid in diagnosis of pheochromocytoma.

Recently, an adrenal tumor was found in a patient with grade 3 hypertension. The mecholyl test had been negative for pheochromocytoma. On microscopic examination of this tumor a report was made of carcinoma in an adenoma of the adrenal cortex.

SUMMARY AND CONCLUSIONS

A case of pheochromocytoma is presented.

The pharmacologic effects of mecholyl, atropine and curare in this patient are described and discussed. Mecholyl produced an initial transitory fall in blood pressure followed by a marked rise to hypertensive

levels. Atropine abolished the muscarinic reactions of mecholyl but failed to influence the rise in pressure. Curare did not affect the response to mecholyl in any way.

A diagnostic test for pheochromocytoma, based on the reaction to 25 mg. of mecholyl given subcutaneously, is described. An initial fall in blood pressure of short duration which is followed by a marked and more sustained rise to hypertensive levels constitutes a positive test. Of twenty-seven control patients receiving mecholyl, none showed this hyper-reactor response.

Comparison between the histamine and mecholyl tests is made. In a group of nine patients, five showed a hyper-reactor response to histamine. It is suggested that the mecholyl test may be more reliable than the histamine test in diagnosis of pheochromocytoma inasmuch as no hyper-reactors were noted among the controls when mecholyl was administered.

From the pharmacologic evidence presented it is deduced that mecholyl directly stimulates the chromaffin tissue of pheochromocytoma.

REFERENCES

1. Beer, E., King, F. H. and Prinzmetal, M. Pheochromocytoma with demonstration of pressor (adrenalin) substance in blood preoperatively during hypertensive crisis. *Ann. Surg.*, 106: 85, 1937.
2. Biskind, G. R., Meyer, M. A. and Beadner, S. A. Adrenal medullary tumor; pheochromocytoma cured by surgical intervention. *J. Clin. Endocrinol.*, 1: 113, 1941.
3. Dolgin, W. Pheochromocytoma and sudden death following injury of the head; report of a case with autopsy. *Arch. Path.*, 40: 135, 1945.
4. Duncan, L. E., Jr., Semans, J. H. and Howard, J. E. Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus; disappearance of diabetes after removal of tumor. *Ann. Int. Med.*, 20: 815, 1944.
5. Evans, W. F. and Stewart, H. J. Peripheral blood flow in cases of adrenal pheochromocytoma before and after operation. *Am. Heart J.*, 24: 835, 1942.
6. Engel, F. L., Mencher, W. H. and Engel, G. L. "Epinephrine shock" as a manifestation of pheochromocytoma of adrenal medulla; report of case with successful removal of tumor. *Am. J. M. Sc.*, 204: 649, 1942.
7. Goodman, L. and Gilman, A. The Pharmacological Basis of Therapeutics. New York, 1941. The Macmillan Company.
8. Heath, F. K., Cahill, G. F. and Atchley, D. W. Pheochromocytoma; correct diagnosis and successful operation. *J. A. M. A.*, 117: 1258, 1941.
9. Hyman, A. and Mencher, W. H. Pheochromocytoma of adrenal gland. *J. Urol.*, 49: 755, 1943.
10. Kirschbaum, J. D. and Balkin, R. B. Adrenalin-producing pheochromocytoma of adrenal associated with hypertension; report of 3 cases. *Ann. Surg.*, 116: 54, 1942.
11. Koster, E. F. Adrenal-sympathetic syndrome associated with paraganglioma of organ of Zuckerkandl. *Ohio State M. J.*, 41: 729, 1945.
12. Kvale, W. F., Roth, G. M., Clagett, O. T. and Dockerty, M. B. Headache and paroxysmal hypertension; observations before and after removal of pheochromocytoma. *S. Clin. North America*, 24: 922, 1944.
13. Le Compte, P. M. Cushing's syndrome with possible pheochromocytoma; report of a case. *Am. J. Path.*, 20: 689, 1944.
14. MacKeith, R. Adrenal-sympathetic syndrome; chromaffin tissue tumour with paroxysmal hypertension. *Brit. Heart J.*, 6: 1, 1944.
15. Mayo, C. H. Paroxysmal hypertension with tumor of retroperitoneal nerve; report of a case. *J. A. M. A.*, 89: 1047, 1927.
16. McCullagh, E. P. and Engel, W. J. Pheochromocytoma with hypermetabolism, report of 2 cases. *Ann. Surg.*, 116: 61, 1942.
17. McGavack, T. H., Benjamin, J. W., Speer, F. D. and Klotz, S. Malignant pheochromocytoma of adrenal medulla (paraganglioma); report of case simulating carcinoma of adrenal cortex with secondary adrenal insufficiency. *J. Clin. Endocrinol.*, 2: 332, 1942.
18. Mortell, E. J. and Whittle, J. P. Pheochromocytoma. Case report with certain observations on the pathologic physiology. *J. Clin. Endocrinol.*, 5: 396, 1945.
19. Neff, F. C., Tice, G. M., Walker, G. A. and Ockerblad, N. Adrenal tumor in female infant with hypertrichosis, hypertension, overdevelopment of external genitalia, obesity, but absence of breast development. *J. Clin. Endocrinol.*, 2: 125, 1942.
20. Nettleship, A. Adrenal medullary tumor; study of chromaffin cell tumor of adrenal. *J. Clin. Endocrinol.*, 1: 124, 1941.
21. Roth G. M. and Kvale, W. F. Tentative test for diagnosis of pheochromocytoma. *Proc. Cen. Soc, Clin. Research*, 17: 18, 1944; *J. Lab. & Clin. Med.*, 30: 366, 1945.
22. Roth, G. M. and Kvale, W. F. Tentative test for pheochromocytoma. *Am. J. M. Sc.*, 210: 653, 1945.
23. Soffer, L. J. Diseases of the Adrenals. Philadelphia 1946. Lea and Febiger.
24. Soffer, L. J., Mencher, W. H. and Colp, R. Pheochromocytoma of the adrenal gland. *S. Clin. North America*, 26: 368, 1946.
25. Strickler, C. W., Jr., Pheochromocytoma; operative failure; case report. *South. Surgeon*, 11: 193, 1942.
26. Thorn, G. W., Hindle, J. A. and Sandmeyer, J. A. Pheochromocytoma of adrenal associated with persistent hypertension; case report. *Ann. Int. Med.*, 21: 122, 1944.

Absorption and Metabolism of Lipiodol after Oral Administration*

Method for the Study of Fat Absorption and Fat Metabolism in Man

J. GROEN, M.D.
Amsterdam, Holland

ABSORPTION of fat in the small intestine is usually estimated either by microscopic examination of the feces or by determination of the fat content of the dried stools. Some investigators prescribe a diet of known composition during the test. The method has been improved by Van Hees[1] but is still not satisfactory. The main objection is that it is impossible by this method to distinguish between exogenous fat, the lipoids that occur normally in the stools, and fatty acids of low molecular weight that are formed inside the intestine from other compounds.

Van Creveld[2] has used iodized fat, iodipine, for the study of fat absorption. After oral administration of this substance he made qualitative tests for the presence of inorganic iodine in the urine. Trémolières and Cheramy[3] determined the iodine excretion in the urine of the first twenty-four hours after ingestion of lipiodol as a measure of fat digestion. Pansdorf[4] followed by roentgenograms the disappearance of an emulsion of iodipine which had been introduced through a duodenal tube. In 1936 Formijne[5] used iodized fatty acids to study their transport from the small intestine into the mesenteric lymphatics. Kuster[6] used iodipine to demonstrate that the intestine of infants absorbs emulsified fats better than fats in a non-emulsified condition.

For the present investigation we used Lipiodol Lafay, a heavy liquid preparation of iodized poppy-seed oil. In this preparation the iodine is in firm chemical combination as evidenced by the negative results of all tests for inorganic iodine. Its high specific gravity (1.35) makes it possible by roentgen studies to follow its passage into the stomach and small intestine after it has been administered by mouth. In normal people the lipiodol shadow gradually disappears as absorption of the fat proceeds. When fat absorption is impaired, a considerable part of the contrast medium remains visible in the x-ray films; it escapes absorption in the small intestine and may produce a contrast picture of the colon. This furnishes us with the possibility of a roentgenologic function test for estimating the efficacy of the absorption of fat. In addition, quantitative estimation of iodine appearing in the stools after administration of lipiodol is a chemical test for the absorption function of the intestine which can be carried out simultaneously. Finally, the amount of inorganic iodine which is excreted in the urine serves as a yardstick of the metabolism of lipiodol after its absorption, and through this we may gain insight into the metabolism of ingested fat.

METHOD

It is necessary to exclude from the test those patients who are hypersensitive to iodine. For this reason 0.5 Gm. of potassium iodide is administered to the patient on the evening before the test. Next morning the patient is seen and special attention is paid to rashes, colds, rhinitis, headache, conjunctivitis, etc. The test is carried out only if these symptoms are absent.

At 7:30 A.M. the patient receives a breakfast

* From the Department of Medicine of the Wilhelmina-Gasthuis, Amsterdam, Holland. With the technical assistance of Miss N. ten Bruggencate and Miss G. C. Mager.

consisting only of two biscuits and 300 cc. of tea. At the same time a mixture is given of 10 cc. Lipiodol Lafay (so-called "descending" lipiodol, said to contain 40 per cent iodine) and 10 cc. olive oil.

This quantity contains 4.2 Gm. of iodine.* Addition of olive oil is necessary as the undiluted lipiodol is of such heavy consistency that it is difficult to swallow. It would also remain too long inside the stomach. Between 7:30 and 12:00 no food is taken and during the test no drugs are given. In preliminary experiments x-ray studies of the intestinal tract were made at short intervals. It appeared that a satisfactory picture of the course of the absorption could be obtained by taking x-rays at two, three and one-half, five, eight and ten hours, respectively, after administration of the contrast medium.

All urine and feces are collected, including those of the night before the test, after potassium iodide has been given. In the beginning the iodine content of feces and urine was separately determined in twenty-four-hour samples. Later a single determination of the total excretion appeared to be sufficient. For this purpose the urine was stored in large bottles. After twelve days the total quantity was measured and the iodine content was determined in an aliquot sample. The feces were also collected, weighed, mixed by shaking in a special shaker by means of which a homogeneous mixture could be obtained, and the iodine determined in a weighed aliquot. The largest quantity of iodine is excreted during the first eight days after the test; after this only small quantities of iodine appear in the feces and urine. It was found that by terminating the collection of feces and urine after twelve days no error was made. In cases in which speed is required it is justifiable to terminate the collection of the excreta after eight days.

Determination of the iodine content was made by the method of Mathews.[7] A weighed quantity of feces or urine is heated with chromic acid and sulfuric acid by which all iodine is oxidized to iodate. The oxidation flask is connected to a special distilling apparatus and the iodate is reduced by addition of phosphorous acid to hydriodic acid and free iodine. These are distilled and received in a solution of potassium carbonate and sulfurous acid at which time they are transformed into potassium iodide. At the end of the distillation bromine is added. The excess of bromine is removed by boiling and the potassium iodate which has been formed is titrated with sodium thiosulfate after addition of potassium iodide and acetic acid. Inorganic iodide and lipiodol added to urine and stools were quantitatively recovered by this method.

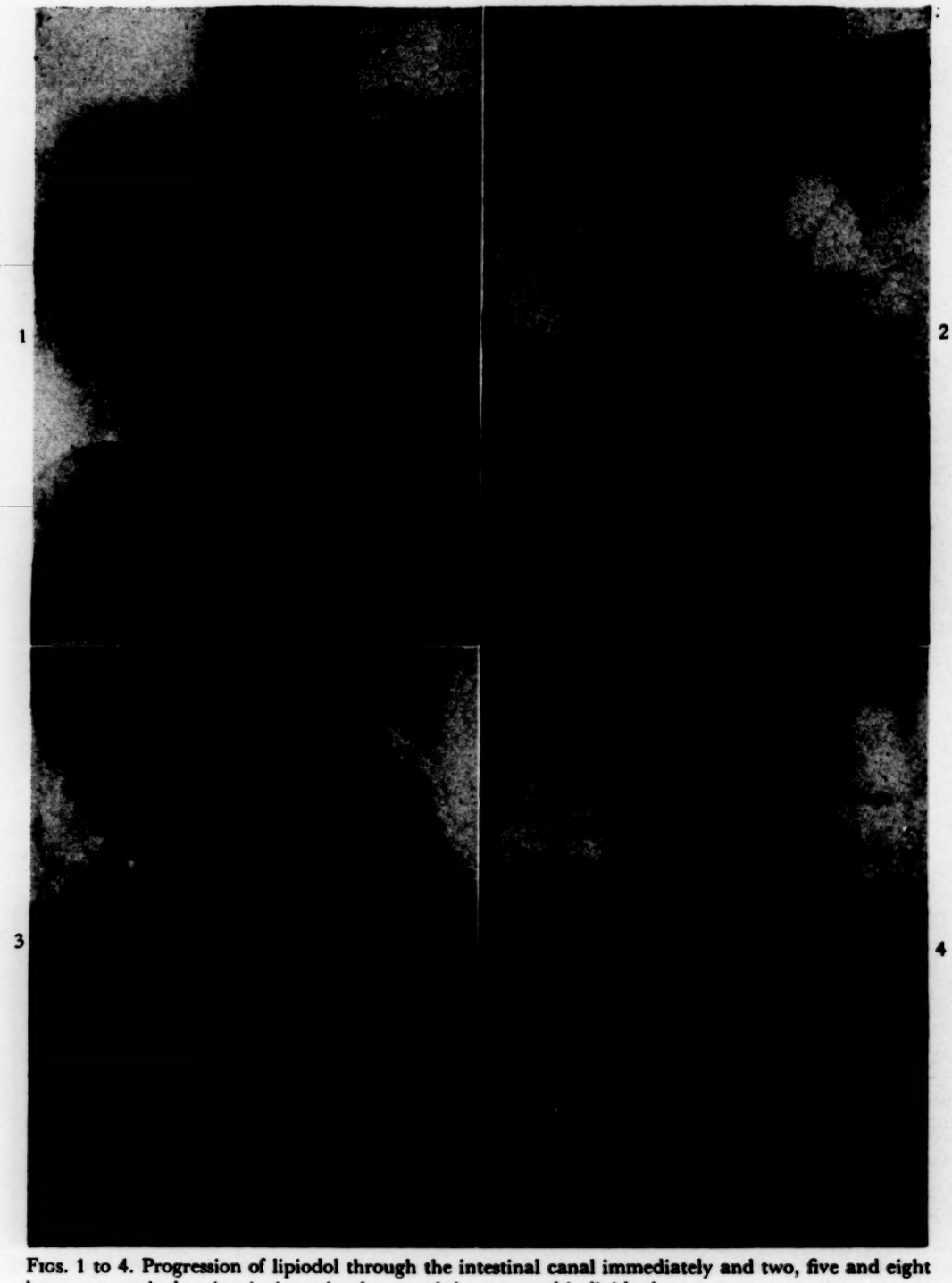
* According to the manufacturers, 10 cc. of lipiodol should contain 5.4 Gm. of iodine. However, in the samples of lipiodol used by us we found only 4.2 Gm. (The American product is standardized to meet U.S.P. requirements of 540 mg. iodine per cc.)

RESULTS OF THE ROENTGENOLOGIC STUDIES

In Normals. Immediately after the lipiodol is swallowed the contrast medium is seen to form large drops along the mucous membrane of the stomach where they gradually merge into a relief picture of the mucous membrane.* (Figs. 1 to 4.)

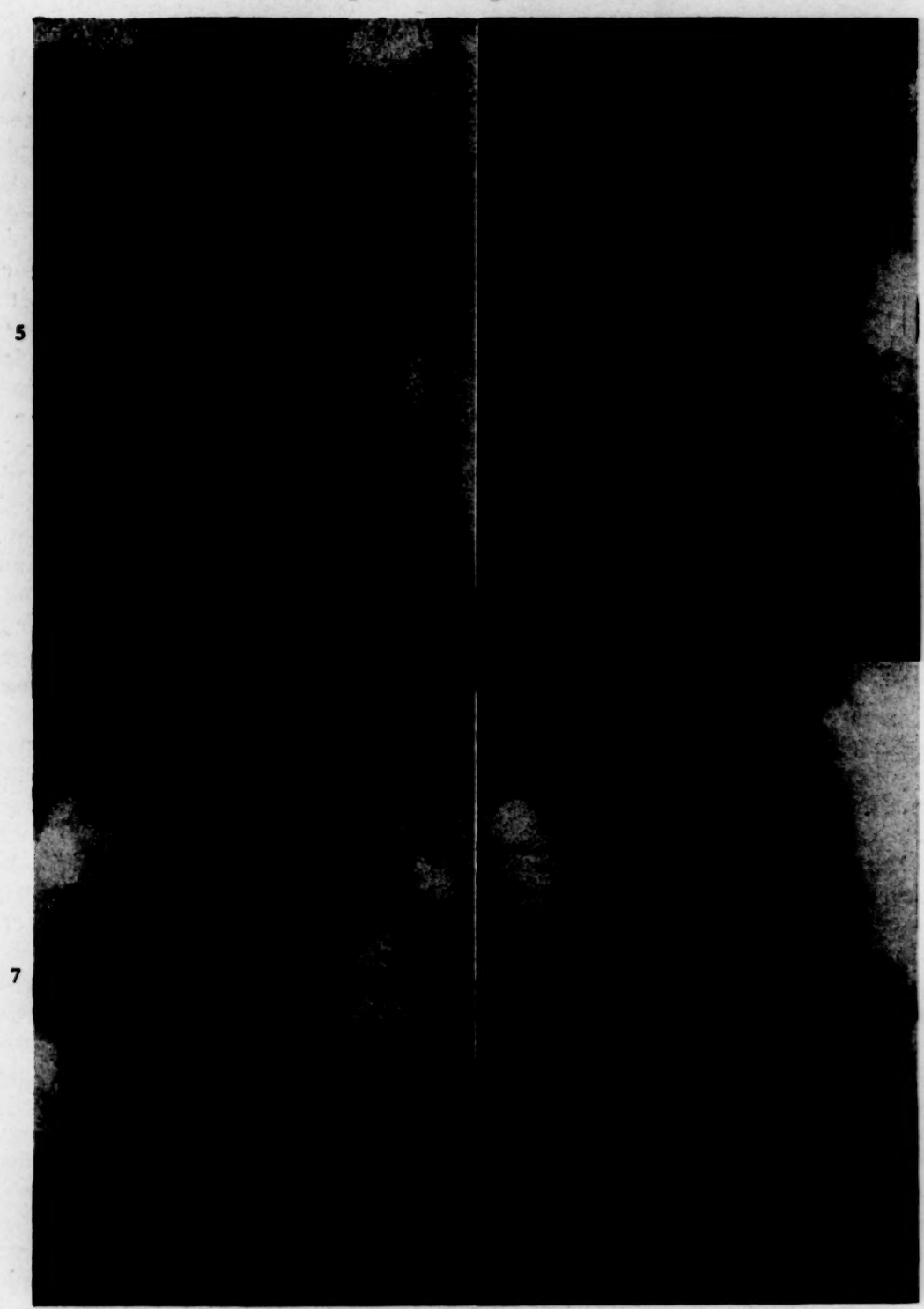
After about one-half hour the lipiodol appears in the duodenum where it gives a distinct picture of the Kerckring's folds. Then the contrast medium enters the jejunum. In almost all subjects the stomach is nearly emptied after two hours and completely so after three and one-half hours. In the duodenum small amounts giving sharp contrast are still present after two hours. After two hours most of the lipiodol is found in the jejunum as small scattered flakes. (In some cases we found the lipiodol after two hours for the greater part in the ileum.) After three and one-half hours more than one-half of the oil is absorbed and much less lipiodol is visible in the x-ray picture than after two hours. At the same time the image appears less distinct owing to dilution and emulsification of the lipiodol. After five hours very little of the contrast medium is left. A little lipiodol may be present in the cecum. One of the characteristics of normal lipiodol absorption is that only a very small part of the contrast substance reaches the cecum. It is noticeable that the small residue present in the lower part of the ileum and in the cecum gives sharper contrast than in the former plates when the entire amount of lipiodol was in the small intestine. This is probably due to concen-

* This relief picture has not been further studied in the present investigation. It would be worth while to compare the "fat relief picture" of the stomach with that obtained after administration of a barium meal.



FIGS. 1 to 4. Progression of lipiodol through the intestinal canal immediately and two, five and eight hours, respectively, after its ingestion by mouth in a normal individual.

tration of the contrast medium in the lower part of the intestine by absorption of water. After eight hours the small intestine is completely empty. The few drops of lipiodol which have reached the large intestine are seen as small spots in the ascending colon but the contrast is poor. After ten hours the x-ray shows a normal picture so that anyone examining the film without knowledge of the administration of a contrast medium would see nothing unusual except, after eight and ten hours, a shadow in the region



Figs. 5 to 8. Progression of lipiodol through the intestinal canal immediately and two, five and eight hours, respectively, after its ingestion by mouth in a case of non-tropical sprue.

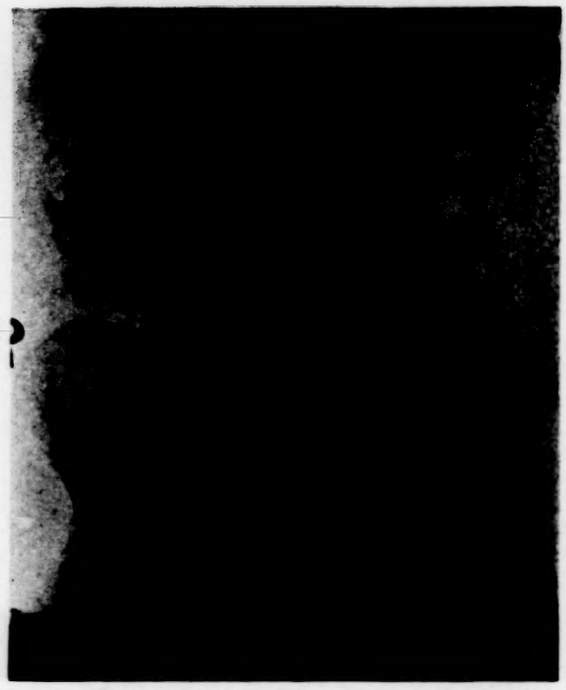


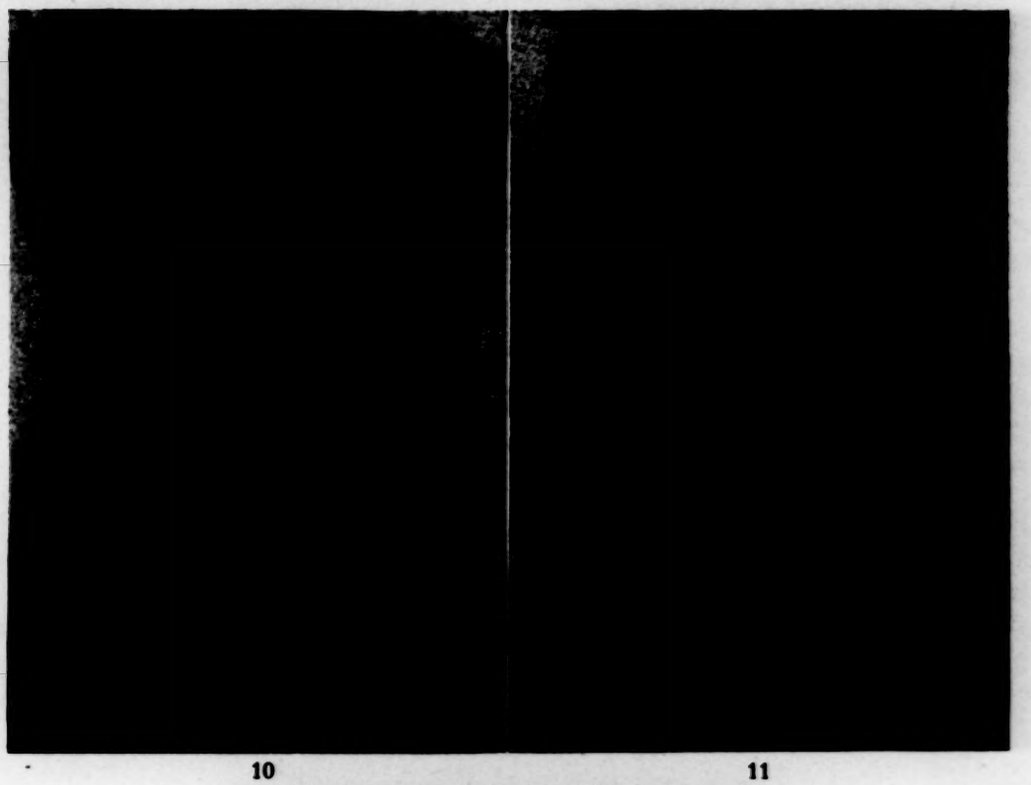
FIG. 9. Contrast picture of the colon ten hours after ingestion of lipiodol by mouth, indicating diminished absorption in a case of tropical sprue.

of the urinary bladder. This is due to the high specific gravity of the urine in which part of the lipiodol iodine is excreted as inorganic iodine.

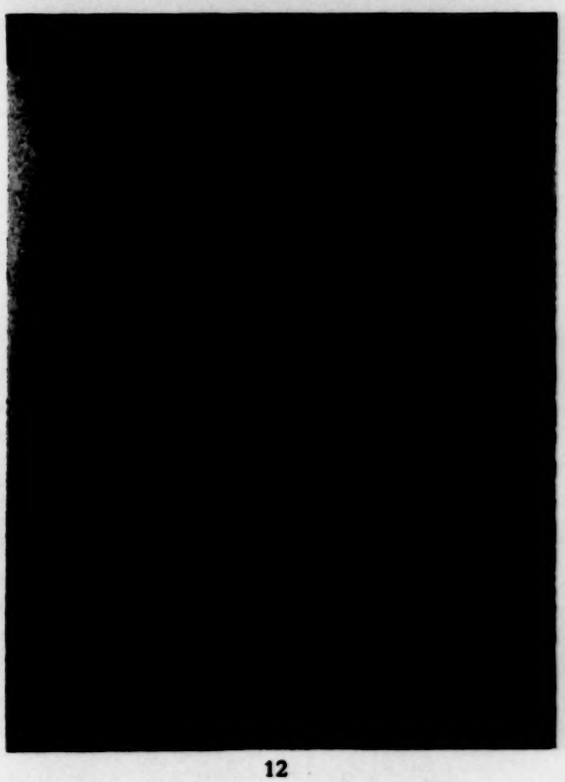
In Patients with Various Pathologic Conditions. Normal results of the tests were obtained in various disease conditions. In two patients with anorexia nervosa with extreme emaciation the lipiodol picture was normal. In a third patient, in whom the diagnosis of pituitary cachexia was made, normal results of the lipiodol test proved that the extreme emaciation of this patient was not caused by diminished absorption of ingested fat. One patient with adiposity, showed normal fat absorption. One subject with anorexia nervosa also had achylia gastrica. This apparently had no influence upon the absorption of lipiodol, which was normal. The same was observed in a patient with achylia gastrica with hypochromic anemia, in whom a normal lipiodol absorption also was found. Two patients with typical duodenal ulcer with high acid content of the stomach and one with uncomplicated cholelithiasis also had normal fat absorption.

Most interesting were the x-ray studies of the absorption of lipiodol in tropical and non-tropical sprue. We were able to examine six patients. In all cases an abnormal x-ray picture was obtained. The lipiodol left the stomach in the normal time. However, after two, three and one-half and five hours abnormally large quantities of lipiodol were still present in the small intestine. In all these patients the cecum filled with an abnormal amount of lipiodol which in some cases produced an excellent relief picture of the colon by the unabsorbed iodine-containing fat. (Figs. 5 to 9.) The disturbance in fat absorption was not equally pronounced in all patients. Two patients with non-tropical sprue were examined before and after treatment with a diet rich in protein and poor in fat and large doses of liver extract. In both cases the lipiodol test showed definite improvement after this therapy. In one case of tropical sprue the absorption even became completely normal after treatment.

Figures 10 to 12, the pictures of a patient with tuberculosis of the small intestine, show that after three and one-half to five hours large quantities of lipiodol were still present in the small intestine; after eight hours complete filling of the colon was obtained. Evidently in this case a large part of the lipiodol had escaped absorption in the small intestine. In contrast to this, in two patients with tuberculosis of the peritoneum (without diarrhea) normal lipiodol pictures were obtained. One patient with a gastrojejunocolic fistula (Figs. 13 to 15) was studied. Immediately after entering the stomach the lipiodol was seen to divide into two parts, one of which reached the small intestine via the gastroenterostomy opening; the other part almost immediately reached the descending colon from the stomach. Of the lipiodol passing through the small intestine, a smaller quantity than normal was absorbed. Evidently the disturbed fat absorption in cases of gastrojejunocolic fistula is caused not only by the fact that part of the food immediately reaches the colon, but also by disturbed absorption of



10 11



12

FIGS. 10 to 12. Progression of lipiodol through the intestinal canal two, five and eight hours, respectively, after its ingestion by mouth in a case of intestinal tuberculosis.

13 14

15

FIGS. 13 to 15. Progression of lipiodol through the intestinal canal one-fourth, two and eight hours, respectively, after its ingestion by mouth in a case of gastrojejunocolic fistula.

that part of the food which passes through the small intestine. A marked impairment of fat absorption was found in a patient with pancreatic insufficiency. This was a patient with a common duct stone. At operation the stone was found so firmly impacted in the papilla Vateri that it was decided to leave it there and to make a palliative anastomosis between the gall-bladder and the stomach. After operation the jaundice cleared but the patient was troubled with fatty stools. The disturbance in fat absorption is illustrated in Figures 16 to 18.

Three patients with ulcerative colitis were examined. In one, the disease was mild and of short duration. Here the lipiodol picture was almost normal. In two patients who had been suffering from the disease for a long time and who were in poor general condition, the roentgenologic picture after eight hours showed an excessive amount of unabsorbed lipiodol. This disturbed absorption of fat in patients with ulcerative colitis is of great importance. It is due to a disturbance of the ileum which can sometimes be verified by "routine" x-ray examination by means of a barium meal. Many patients with long-standing ulcerative colitis show an abnormal picture of the last loop of the ileum. It is important to keep this disturbed absorption in mind, especially in connection with the therapy of ulcerative colitis.

We examined four patients with pernicious anemia in relapse. In all, an impaired absorption was demonstrated roentgenologically. However, the impairment was not so pronounced as in those with sprue. These facts, together with earlier findings,[8] make it probable that impaired absorption contributes toward development of deficiency in pernicious anemia.

CHEMICAL STUDIES

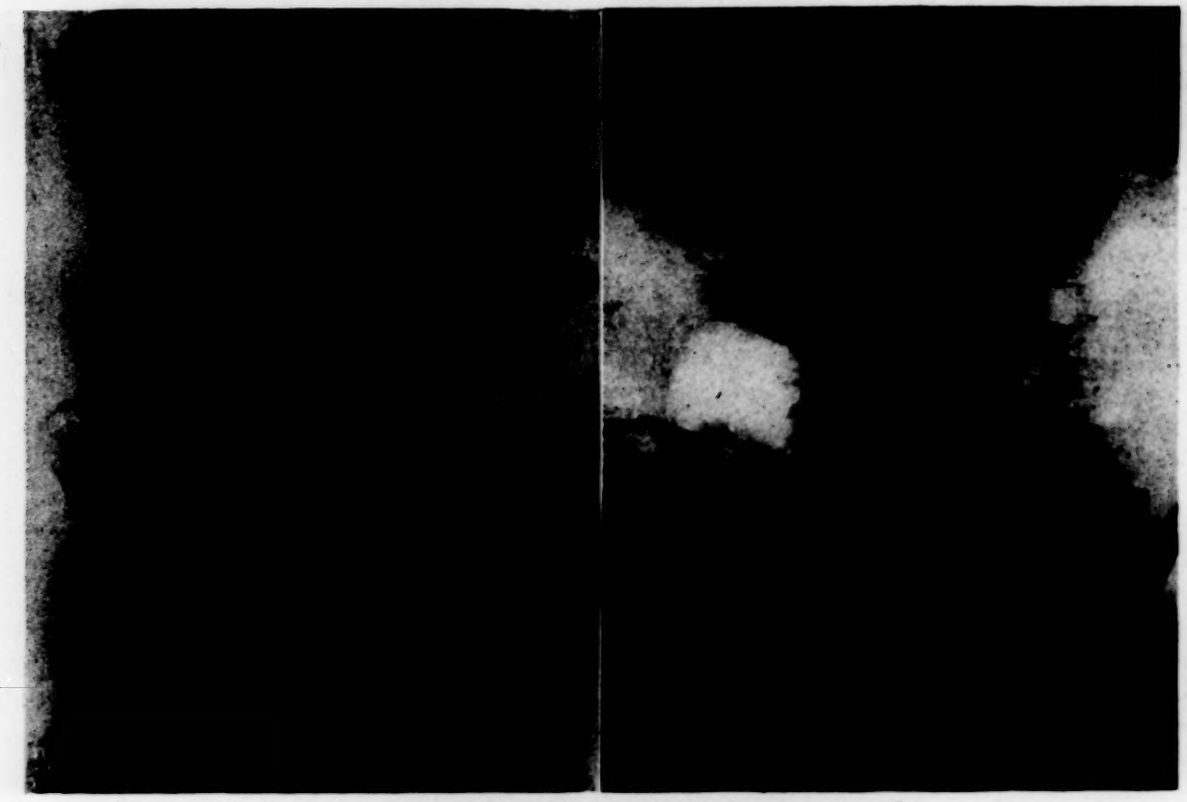
After administration of lipiodol, iodine is always found in the feces. This iodine seems to be present in organic form only, for when the feces are shaken with water we never found iodine after addition of nitric acid followed by addition of starch or extracting with chloroform. Also after incubation of lipiodol with gastric juice, duodenal juice or a feces suspension we never found free iodine. When the feces were dried and extracted with ether, 80 per cent of the iodine content passed into the ether. On shaking the feces emulsion with ether after acidifying with hydrochloric acid, all the iodine passed into the ether. Apparently non-absorbed lipiodol is present as neutral fat or as fatty acid to the extent of about 80 per cent and about 20 per cent as soaps. The urine always contains inorganic iodine after the test.

In our first investigations the iodine contents of the urine and feces were determined daily. The curve of the iodine excretion shows a definite course. During the first four to seven days the excretion in the urine and feces increased rapidly, after this the daily output diminished gradually. After eight to eleven days the excretion was usually reduced to a few mg. of iodine per day.[9]

The iodine administered as lipiodol was always 4.2 Gm.; on the evening before the test the patient received 0.5 Gm. of potassium iodide which contains 0.383 Gm. inorganic iodine. Control studies in normal individuals and in patients with sprue who received only 0.5 Gm. of potassium iodide without lipiodol revealed that this inorganic iodine is almost completely absorbed and excreted in the urine so that all the iodine found in the feces after the test may be considered to be derived from the lipiodol.

Results of the determinations of iodine in the stools are given in the first column of Table 1, expressed as percentages of the amount of iodine administered as lipiodol. The second column gives the percentage of lipiodol iodine absorbed (by subtraction). The third column indicates the percentage of iodine recovered from the urine.

Excretion with the Feces. After administration of 4.2 Gm. of lipiodol iodine, normal persons were found to excrete only 100 to 400 mg. of iodine with the feces, which



16 17

18

FIGS. 16 to 18. Progression of lipiodol through the alimentary canal two, eight and twenty-four hours, respectively, after its ingestion by mouth in a case of pancreatic insufficiency.

means that in normal circumstances 2 to 9 per cent of lipiodol escapes absorption.

In sprue the quantities of lipiodol lost with the feces were much greater. In five patients with non-tropical sprue the iodine content of the feces varied between 807 mg. (19.2 per cent) and 1,899 mg. (77.2 per cent). In two subjects with non-tropical sprue considerable improvement was obtained by treatment with diet and liver extract; however, the absorption did not become quite normal. This is in agreement with the well known fact that non-tropical sprue can be greatly improved but not completely cured by therapy.[10] In one patient with tropical sprue who was examined after treatment normal absorption of the lipiodol was found.

TABLE 1*

IODINE OUTPUT IN FECES AND URINE AFTER ORAL ADMINISTRATION OF LIPIODOL (4.2 GM. IODINE)

Name	Diagnosis	Iodine in Feces %	Iodine Absorbed %	Iodine in Urine %	Iodine Retention %	Remarks
K. K.	Normal	7.8	92.2	17.1	81	
Te.	Normal	1.8	98.2	31.7	68	
Sn.	Normal	6.7	93.3	7.7	82	
G.	Normal	2.9	97.1	52.7	45	Losing weight
B.	Normal	8.5	91.5	37.7	59	On a reducing diet
R.	Sprue	77.2	22.8	4.6	85	
R.	After treatment	47.8	52.2	19.5	62	
v. d. S.	Sprue	36	64	24.8	61	
P.	Sprue	19.2	80.8	5.8	92	Mild case
W.	Sprue	45	55	9.6	82	
W.	After treatment	27.6	72.4	17.1	77	
N.	Sprue	31.2	68.8	4.3	93	
v. O.	Tropical sprue (after treatment)	1.6	98.4	62.4	37	
H.	Obstructive jaundice	33	67	1.4	98	Diet poor in fat
A.	Obstructive jaundice	39.5	60.5	5.9	92	Diet poor in fat
T.	Gastrojejunocolic fistula	51.6	48.4	20.9	58	
B.	Fistula of ileum	18.3	81.7	78.5	4	Losing weight
v. d. W.	Tuberculous peritonitis	6.6	93.4	48	48	
L.	Intestinal tuberculosis	36	64	26	59	
P.	Ulcerative colitis	15	85	53.7	36	Losing weight
B.	Ulcerative colitis	15.4	84.6	54	36	Losing weight
N.	Ulcerative colitis (proctitis)	6	94	28	71	
O.	Pernicious anemia	10	90	44.4	50	
S.	Pernicious anemia	3.1	96.9	20.6	78	
Sp.	Pernicious anemia	5	95	53	44	
H.	Pernicious anemia	12	88	63.4	28	
F.	Resected stomach	29.8	70.2	32.6	54	With pernicious anemia
B.	Resected stomach	5.7	94.3	40	57	
S.	Gastro-enterostomy	20.7	79.3	29	64	
v. K.	Castor oil	40.7	59.3	4.4	92	Gaining weight
H.	Paraffin liquid	45.5	54.4	30.7	87	Gaining weight
K.	Normacol	9	91	40.4	56	
G.	Cholelithiasis	9.2	90.8	53.3	42	
O.	Cholecystectomy	18.6	81.4	28	66	
S.	Paget's disease	1.5	98.5	45.7	54	
P.	Gaucher's disease	10.8	89.2	78.1	12	Losing weight

* The first three columns give the quantity of iodine as percentage of the ingested amount; the retention is given as percentage of the quantity that was actually absorbed.

Severely disturbed absorption was found in patients with obstructive jaundice. We examined two patients with carcinoma of the papilla Vateri. Both showed a markedly increased excretion of iodine in the feces (1.660 and 1.387 Gm. respectively). In these

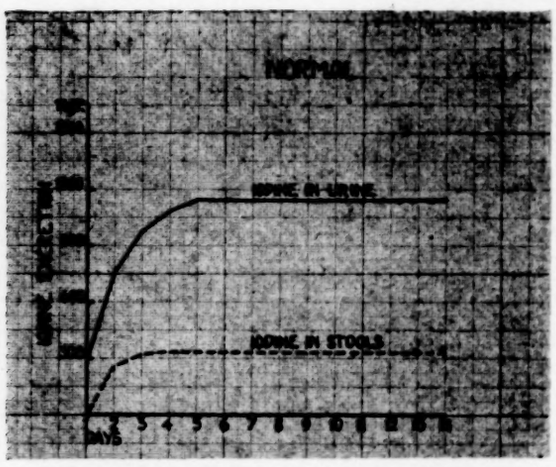


FIG. 19. Excretion of iodine in urine and stools after ingestion of lipiodol by mouth in a normal subject; iodine excretion in the urine exceeds the excretion in the stools.

cases, instead of 91 to 98 per cent, only 60 per cent and 67 per cent of the fat was absorbed.

The absorption of fat was also markedly disturbed in the patient with gastrojejunocolic fistula and in a patient with surgical anastomosis of the ileum. One patient with tuberculosis of the peritoneum had a normal absorption whereas in a patient with intestinal tuberculosis a distinct disturbance was found. Two of four patients with pernicious anemia had a normal, two others an increased iodine content in the feces. One patient, who ten years previously had a resection of the stomach, was examined and found to have pernicious anemia. Examination with lipiodol proved that a disturbed fat absorption was present; the feces contained 1.253 Gm. of iodine, i.e., only 70 per cent had been absorbed. Another patient with a resected stomach had a normal fat absorption whereas a patient with a gastroenterostomy had a disturbed excretion (20.7 per cent in the feces).

Three patients suffering from ulcerative colitis were examined, two of whom were severely ill. These two had disturbed absorption. In the other patient, in whom the disease was mild and restricted to the rectum, a normal absorption was found.

It appeared that lipiodol is not as well absorbed when given with a laxative. In one case we gave a normal test person the lipiodol together with one tablespoonful of liquid paraffin. A second normal person received 150 cc. of 5 per cent magnesium sulfate solution and a third an agar preparation (normacol) simultaneously with the lipiodol. The first and second patient showed diminished fat absorption. This observation indicates that laxatives should not be given together with other medicaments or during meals as this may impair the absorption, especially of fat, fat-soluble vitamins and drugs.

Special attention must be given to the result in a patient with Paget's disease. In this patient we found the smallest iodine content of the feces which we have encountered so that excellent absorption was apparently present. In this connection it is noteworthy that Althausen[11] discovered rapid absorption of galactose in a patient with Paget's disease.

Excretion in the Urine. In normal individuals in whom the bulk of lipiodol is absorbed, excretion of iodine in the urine is much higher than in the feces. This situation is reversed in the severely disturbed absorption in cases of sprue. These patients excrete more iodine in the feces than in the urine. (Figs. 19 and 20.)

The amount of iodine excreted in the urine appeared to differ widely both in normal individuals and in the patients. The variation is due in the first place to a difference in absorption, but even after lipiodol has been absorbed its fate in the body differs in different individuals. Part of it is stored in the body, part of it is oxidized. It is only on oxidation that inorganic iodine is liberated from lipiodol. The amount of inorganic iodine which is set free, therefore, may furnish us with a yardstick to measure the amount of the oil which has been oxidized and by inference may give us an insight into the mechanism which determines the proportion of food fat which is oxidized compared with the amount which is stored.

Retention of Iodine. In the third column of Table 1 the percentages of retained iodine are given. They were calculated by sub-

FIG. 20. Excretion of iodine in urine and stools after ingestion of lipiodol by mouth in a case of non-tropical sprue; iodine excretion in the stools exceeds the excretion in the urine.

tracting from the urinary iodine 0.383 Gm., the amount derived from the potassium iodide given the evening before the test. The figure thus obtained is expressed as a percentage of the amount of iodine absorbed from the lipiodol. It is assumed to indicate the percentage of lipiodol which has been oxidized. One hundred minus this figure is regarded as retained. As the body possesses only a limited capacity for storage of inorganic iodine it may be safely assumed that the percentage of iodine retained represents the percentage of ingested fat stored.

The number of patients examined under different circumstances has not been large enough to allow of definite conclusions about the various mechanisms that determine the relative proportion of ingested fat which is utilized and stored. First among the factors that appeared to influence the storage of fat is the caloric balance of the body. Normal persons and patients who at the time of the test were putting on weight exhibited marked retention of lipiodol. Individuals who were losing weight retained much less, among them a normal woman who followed a reducing diet while she was undergoing the test. A second factor appeared to be the relative proportion of fat in the diet. We found very great retention in the two patients with obstructive jaundice and in some of our patients with sprue, all of whom were on a diet that was particularly poor in fat.

CRITICAL APPRAISAL OF THE METHOD

Examination of the absorption of lipiodol by means of x-rays and the excretion of iodine in the feces is a useful method for the study of fat absorption. However, it cannot be denied that the method has its disadvantages. The apparatus is rather complicated, the test is rather expensive. The test cannot be carried out in patients who are hypersensitive to iodine. In severely ill patients the test cannot be performed. Furthermore, it is often difficult to evaluate the x-ray film in patients with slight disturbances in absorption. Moreover, it must be kept in mind that the absorption determined in this way is more the result of the collaborating functions of all digestive organs (emptying of the stomach, excretion of bile and pancreatic juice, digestive activity, velocity of passage through the intestine, passage through the intestinal villi, phosphorylation, etc.) than a function test of the isolated absorptive capacity of the intestinal canal.

In interpreting the results we must point to the fact that a disturbed fat absorption

need not be accompanied by diminished absorption of other food substances. Finally, it seems too early to judge the usefulness of the method for estimation of the tendency of the body metabolism towards fat utilization or storage.

SUMMARY

1. The author describes a method for study of the absorption of fat and of its subsequent metabolism. In the test the fate of an iodized oil (lipiodol) after oral administration is followed by: (1) The disappearance of the contrast shadow from x-ray films of the intestinal tract taken at regular intervals; (2) the determination of iodine excretion in the stools; (3) the determination of the amount of iodine excreted in the urine.

2. Normal absorption of lipiodol was found in achlorhydria, duodenal ulcer, uncomplicated cholelithiasis, tuberculosis of the peritoneum, obesity and anorexia nervosa.

3. Diminished fat absorption could be demonstrated in sprue, obstructive jaundice, intestinal tuberculosis, severe ulcerative colitis, gastrojejunocolic fistula, pancreatic insufficiency, in some cases of pernicious anemia and sometimes after stomach operations. The impaired absorption in nontropical sprue improved but did not become completely normal after treatment with diet and liver extract. Administration of laxatives with lipiodol had an unfavorable influence on absorption.

4. Excretion of iodine in the urine after administration of lipiodol by mouth is not a good measure of absorption. It may, however, give insight into the relation between the quantity of ingested fat which is oxidized and the amount which is stored under different circumstances.

Acknowledgment: The author is greatly indebted to the late Dr. A. Grunbaum for much valuable help and advice with the chemical part of the work.

REFERENCES

1. Van Hees, C. De steatorrhoe en haar klinische beteekenis. Thesis, Leiden, 1937.
2. Van Creveld, S. Vetabsorptie by coeliakie. *Nederl. tijdschr. v. geneesk.*, 71: 2015, 1927; 75: 2795, 1931.
3. Trémolières, F. and Cheramy, P. Le lipiodol et le diagnostique des insuffisances pancreatiques. *Concours médical*, 59: 3241, 1932.
4. Pansdorf, H. Röntgenologische Beobachtungen über die Fettverdauung im Magendarmkanal. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 36: 1095, 1927.
5. Formijne, P. Personal communication.
6. Kuster, P. Die Fettverdauung im Säuglingsalter. *Ztschr. f. Kinderh.*, 60: 458, 1938.
7. Matthews, N. L., Curtis, G. M. and Brode, W. R. Determination of iodine in biological materials. *J. Indust. & Eng. Chem., Anal. Sec.*, 10: 612, 1938.
8. Groen, J. The absorption of glucose in deficiency disease. *New England J. Med.*, 218: 247, 1938.
9. Sicard, J. A. and Forestier, J. Diagnostic et therapeutique par le lipiodol. Paris, 1920.
10. Barker, W. H. and Rhoads, C. P. The effect of liver extract on the absorption of fat in sprue. *Am. J. M. Sc.*, 194: 803, 1937.
11. Althausen, T. L., Lockhart, J. C. and Soley, M. H. A new diagnostic test (galactose) for thyroid disease. *Am. J. M. Sc.*, 199: 342, 1940.

Reiter's Syndrome*

A Report on Four Patients Treated with Streptomycin

THOMAS A. WARTHIN, M.D.
West Roxbury, Massachusetts

THE original description of a syndrome occurring in young males characterized by urethritis, conjunctivitis and arthritis was made in 1916 by Reiter[1] in Germany. A number of reports followed in continental literature but it was not until twenty-six years later that Bauer and Engleman[2] first described similar cases in America. During the past two years an increasing number of cases have been recognized and reported in America[2–13] and Great Britain.[14–21] The clinical features of the syndrome have been well described in these papers. However, an analysis of these reports results in the conclusion that as yet a definite etiologic agent has not been determined, nor has a satisfactory treatment been found for this lengthy and often relapsing disease. In this communication four additional cases are reported because of the finding of pleuropneumonia-like organisms in the urine and joint fluid of one case and in the urine of a second case, because unusual myocardial changes were noted, and because of the suggestively promising results of the treatment of this disease with streptomycin.

CASE REPORTS

CASE 1. R. F., a twenty-one year old ex-marine, entered the Veterans Administration Hospital, West Roxbury, Massachusetts, April 15, 1946, complaining of recurrent attacks of urethritis, conjunctivitis and arthritis of one year's duration. Two weeks after sexual exposure in Hawaii, in April 1945, he developed an acute urethritis. Smears were negative for gonococci and the urethral discharge was not affected by treatment with sulfadiazine or penicillin. Approximately one week after the onset his eyes became inflamed, followed by the appearance of a swollen, painful right knee joint. Subsequently the left knee and right ankle were involved and he experienced considerable pyrexia. He was hospitalized for eight months and finally discharged from the Marines, March 5, 1946. On April 3, 1946, a purulent urethral discharge recurred with subsequent dysuria and urinary frequency. On April 5th both eyes became swollen and red. On April 8th his mouth became sore and superficial ulcerations were noted on the glans penis. On April 12th the right knee again became hot, swollen and painful, followed by the same condition in the left knee on the day of admission.

Examination revealed an acutely and chronically ill young male. His temperature was 102°F., pulse 124, respirations 22. The conjunctivae were deeply injected and the lids were crusted with a dried purulent exudate. The lips and adjacent buccal membrane were covered with superficial ulcerations with bloody crusts. The heart sounds at the apex were of a poor quality and the pulse was suggestively dicrotic in character. Eight circinate ulcerations covered the glans penis and there was an abundant purulent urethral discharge from an injected meatus. The prostate gland was normal. Both knees were swollen, hot and very tender. There was marked atrophy of both quadriceps femoris muscles.

Laboratory data revealed a urine containing a trace of albumin and loaded with pus cells. There was a moderate normocytic anemia and polymorphonuclear leukocytosis. The Mazzini and gonococcus complement fixation tests were negative. Repeated cultures and smears of the urethral discharge were negative for gonococci.

* From the Medical Service, Veterans Administration Hospital, West Roxbury, Massachusetts. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

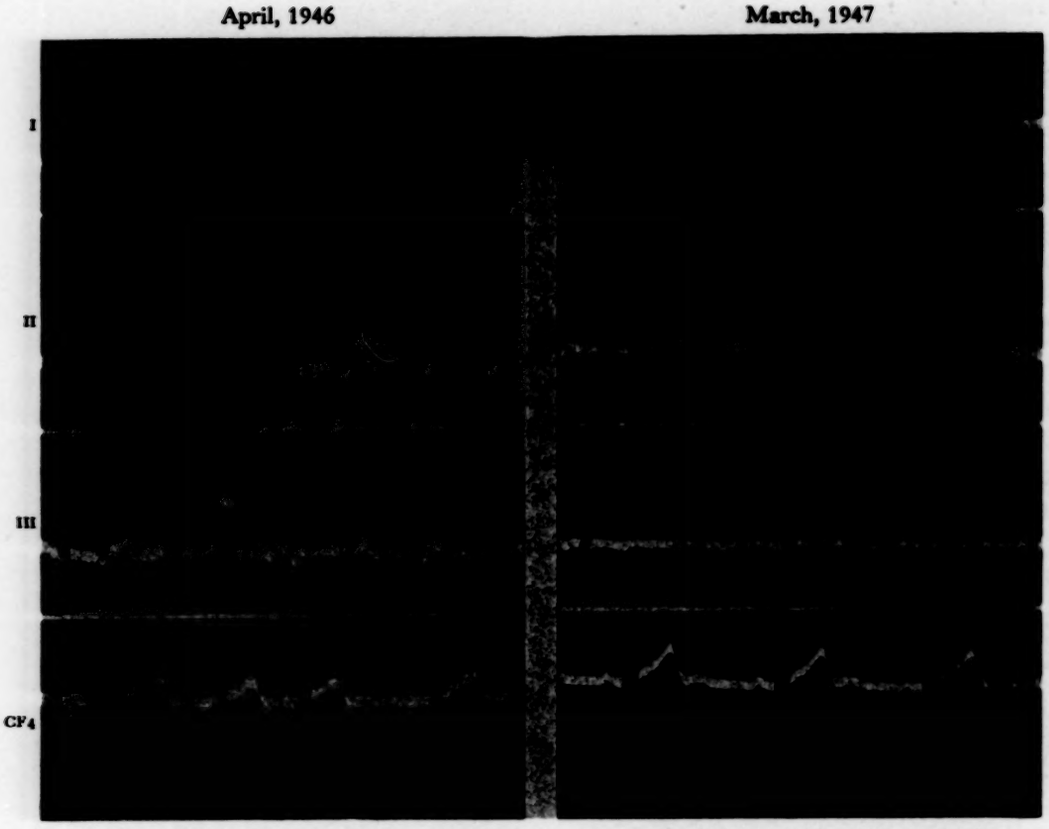


FIG. 1. Case I. The tracing obtained on admission demonstrates second degree heart block with low or inverted T waves in all leads. The electrocardiogram of March, 1947 is within normal limits.

Numerous blood cultures were sterile. Dark field examinations of the penile ulcers were negative. On April 18th urine cultures were made on ascitic agar media. The same day, under careful aseptic conditions and with the patient fasting, the right knee was tapped and 60 cc. of turbid yellow, cloudy fluid was aspirated and cultures made on the ascitic agar media. Further examination of the fluid revealed a 3 plus clot and 32,500 white blood cells, 87 per cent of which were polymorphonuclears. Sedimentation rates varied from 27 to 29 mm. per hour. Both urine and knee cultures subsequently grew out pleuropneumonia-like organisms, the studies being carried out in the laboratory of Dr. Louis Dienes.[27] X-rays of chest and knees were normal. An electrocardiogram (Fig. 1) revealed a P-R interval of .08 to .32 seconds with second degree heart block. The auricular rate per minute was 112 and the ventricular 86, with every third beat dropped. The T waves in leads II and III were inverted. The tracing was interpreted as suggestive of an active myocarditis.

On admission the patient was given penicillin 50,000 units intramuscularly every three hours for five days without improvement of conjunctivitis, urethritis, arthritis or fever. On April 25th streptomycin 0.5 Gm. intramuscularly every three hours was begun and continued through May 1st. During this period a moderate decrease in temperature to 100°F. and pulse to the 80's occurred together with a disappearance of the urethral discharge. Both knees had been tapped twice previously with removal of 40 to 100 cc. fluid. Further joint effusion did not occur and there was marked symptomatic relief. The conjunctivitis disappeared as did the pyuria and dysuria in the course of the week following cessation of the streptomycin. Repeated urine cultures were negative for pleuropneumonia-like organisms. Subsequently the temperature became normal following treatment of the secondary infection of the penile lesions and an accompanying severe regional lymphadenitis. The patient was most enthusiastic about the progress of his condition in comparison with his previous experience. Objectively it must be emphasized that the most striking improvement occurred during the week after treatment rather than during the week of streptomycin therapy,

and coincidental improvement as part of the natural course of the disease is possible.

He began to be ambulatory on May 20th but the severe atrophy of both quadriceps femoris muscles delayed full activity and required prolonged physiotherapy. Convalescence toward full activity was rapid, with loss of anemia and fall in sedimentation rate to 11 mm. per hour. The patient was discharged well, on July 13, 1946, two and one-half months after treatment with streptomycin.

He returned to his work as a construction laborer in September and remained well until March 10, 1947, when he developed a severe diarrhea. This persisted for five days at which time he returned for examination. Nothing noteworthy was found. An electrocardiogram (Fig. 1) was normal and urinalysis revealed only 1 to 2 white blood cells per high power field in the centrifuged sediment. No stool culture was obtained. On March 18, 1947, pain over the left sacroiliac joint and three days later painful swelling over the right first cuneiform bone were noted. These persisted and he was readmitted to the hospital March 24th. Physical examination revealed nothing beyond these changes, conjunctiva, urethra and prostate being normal. The sedimentation rate was again elevated to 22 mm. per hour but urinalyses, urine and prostatic cultures were all negative. X-rays of the affected joints revealed old mild post-traumatic sclerotic changes. He was given physiotherapy and salicylates for two weeks. During this period he continued to experience pain in back, right foot and, in addition, discomfort and slight swelling in his right knee. His oral temperatures were elevated nightly between 99° and 99.6°F. Although no ocular or urinary signs or symptoms appeared, the joint pains persisted unabated. On April 10, 1947, streptomycin therapy, in dosage of 0.5 Gm. every three hours, was begun and continued until April 20th. All joint pains and fever disappeared during the course of therapy and no side reactions were noted. The sedimentation rate remained elevated. Electrocardiograms taken before and during streptomycin therapy were entirely normal. The sedimentation rate fell to 14 mm. per hour on April 30th and he was discharged from the hospital on May 1, 1947. He was able to return to work the week subsequent to his discharge, and when last seen June 17th was in good health.

Case II. J. D., a twenty-three year old ex-sailor, was admitted June 14, 1946, complaining of joint pains, sore eyes and urethral discharge of ten days' duration. The exact date of his last sexual exposure could not be ascertained definitely but was approximately sixteen days prior to onset of symptoms. The triad of complaints appeared simultaneously, the right ankle and hip being the joints involved first, followed in several days by both knees. For four days he had noted chilliness and fever, with severe "canker sores" in his mouth.

There had been a previous attack of balanitis in 1945 and of "rheumatism" at six years of age.

Examination revealed an acutely ill young male in severe distress from joint pain. The temperature was 102°F., pulse 92, respirations 24. Both conjunctivae were injected. There were gray, patchy spots in his mouth covering superficial ulcerations. The foreskin was red, swollen and ulcerated. Partial retraction only could be accomplished but a purulent urethral discharge was evident. Motion was very painful in both knees, right ankle, hip and shoulder. The knee joints contained considerable fluid, more on the left than the right. There was atrophy of the quadriceps femoris muscles.

Laboratory data revealed a urine containing one plus albumin with 10 to 12 white blood cells per high power field in the centrifuged sediment. The leukocyte count was 13,000 with a normal differential count. The Mazzini test was negative. Blood cultures were sterile. Urethral smears and cultures failed to reveal gonococci. The sedimentation rate was 25 mm. per hour on admission and the same rate was noted on July 2nd. Urine culture on ascitic agar on June 20th revealed pleuropneumonia-like organisms, but cultures of straw-colored fluid obtained from both knees were negative. X-rays of the chest and knee were normal.

Penicillin 30,000 units intramuscularly every three hours was started on June 17th and continued until July 1st. Initially there seemed to be some improvement and the temperature fell below 100°F., only to rise again on July 1st. The conjunctivitis cleared during this period and it was not necessary to tap the knee joints again although the patient complained bitterly of joint pain throughout this time. A dorsal slit operation was performed on June 28th to relieve a balanoposthitis. Streptomycin 0.5 Gm. intramuscularly every three hours was begun on July 2nd and continued for seven days. His temperature slowly fell to normal by the end of the week, the urethral discharge ceased and the pyuria cleared. Marked lessening in joint

pain occurred immediately after his treatment had been completed. The patient was allowed up on July 5th and given physiotherapy and special exercises to the atrophied quadriceps femoris muscles. He was walking short distances by July 12th. Recovery was slowed by a Staphylococcus aureus furunculosis of the thighs. He was furloughed home on August 3rd, three weeks after completion of the therapy and finally discharged on August 21st. At that time his sedimentation rate was 14 mm. per hour. Follow-up examination on June 7, 1947, revealed that no symptoms had recurred and he had been working steadily. Urinalysis was normal and the sedimentation rate was 5 mm. per hour.

Case III. L. Z., a twenty-three year old ex-air force lieutenant was admitted May 29, 1946, with a history of urethral discharge and dysuria of three and one-half months' and joint pains of six weeks' duration. On February 14, 1946, nine days after sexual exposure, he had noted purulent urethral discharge. Smears were negative for gonococci and the discharge did not respond to two "courses" of penicillin and sulfonamide tablets. A urologist then treated him with potassium permanganate irrigations and prostatic massage with some diminution in the discharge. However, moderately severe pain on voiding, with urgency, frequency and terminal hematuria developed and persisted. In April both eyes became inflamed and were constantly crusted, this condition lasting about three weeks. For six weeks his hips had been painful and his ankles and right knee had been painful and swollen. For three weeks the left knee had been similarly affected, remaining so until admission. Neoarsphenamine injections at another hospital had not been followed by improvement in joint pain but by lessening in urgency of urination.

Examination revealed a well developed young male who experienced considerable pain in the left knee and both ankles on walking, but otherwise he did not appear ill. The temperature was 99.4°F., pulse 90 and respirations 20. The conjunctivae were normal. Slight urethral discharge was present and the meatus was red. The left lobe of the prostate was irregular but no purulent secretion was expressed on massage. The left knee was swollen and warmer than the right. A small effusion was present in that joint. Both ankles were puffy and painful on weight bearing.

Laboratory data revealed a urine containing a trace of albumin and 70 to 80 white blood cells per high power field. The blood counts were within normal limits. The Mazzini test was negative. Sedimentation rates averaged 21 mm. per hour. A blood culture, urine culture and urine following prostatic massage plated on blood and ascitic agar were all sterile. X-rays of the chest and left knee were normal.

The patient was observed for seven days on symptomatic therapy consisting of salicylates, without improvement in joints or urine. He was started on a week's course of streptomycin 0.5 Gm. intramuscularly every three hours on June 6th. During the week of therapy the urethral discharge disappeared, the urine became negative and the effusion cleared from the left knee. No further elevation in temperature was noted and the patient was completely ambulant with a rare twinge in his ankles. The sedimentation rate was still 19 mm. per hour at the time of discharge from the hospital on June 20th, one week after completion of streptomycin therapy. It was 6 mm. per hour on July 2nd and 7 mm. per hour on August 6th, at the time of follow-up examinations. On those dates the urine was also noted to be free of albumin and white blood cells. The patient then returned to college and when last seen January 3, 1947, had experienced no symptoms suggestive of a recurrence.

Case IV. D. B., a twenty-three year old college student, was referred to the Veterans Hospital by his college infirmary on May 2, 1947. Approximately two weeks after sexual exposure in 1943 he had noted onset of an urethral discharge. Smears were negative for gonococci and the discharge cleared spontaneously. He was then well until May, 1946, when spontaneous gross hematuria occurred. Investigation failed to reveal any cause for this bleeding. The hematuria recurred on at least three occasions in June and July. In September, after repeated sexual exposures, a purulent urethritis developed; and although smears were again negative for gonococci, the discharge cleared after a week's treatment with penicillin. He was well until the middle of March, 1947, when a purulent discharge with slight dysuria again appeared and persisted in spite of treatment with various urinary antiseptics. Three weeks later marked dysuria, frequency and urgency of urination developed. Coincidentally, there was a painful swelling of the left knee.

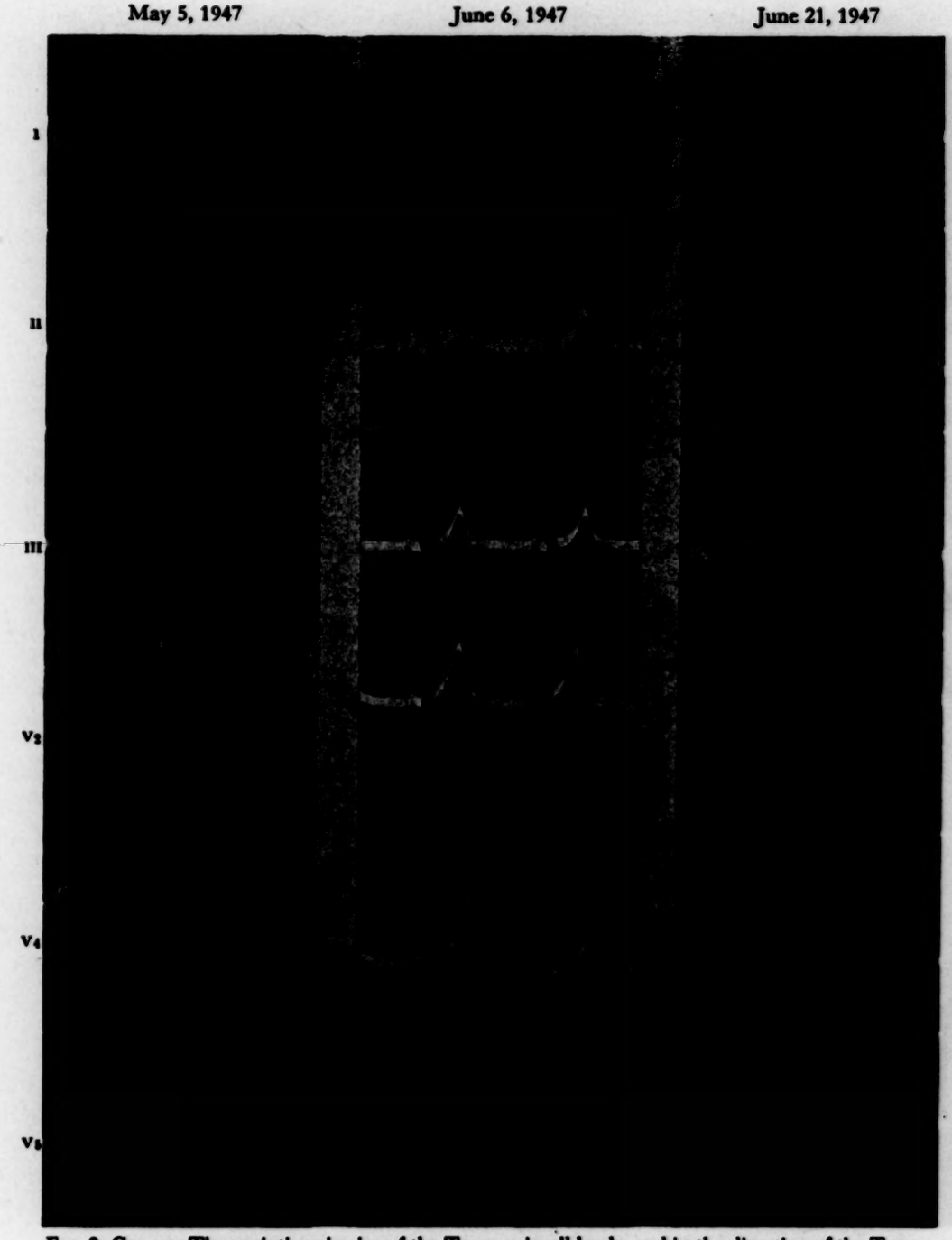


FIG. 2. Case IV. The variations in size of the T waves in all leads, and in the direction of the T waves in lead I are shown during the periods of acute illness, convalescence and clinical recovery.

Later the right knee became involved and he was hospitalized at his college infirmary with a high fever. No cultures for L organisms were carried out either on the urine or synovial fluids. On April 20th he was started on a course of penicillin, 50,000 units every three hours. Three days later it was noted that he had developed a moderate bilateral conjunctivitis which persisted. The dysuria cleared rapidly but the knees continued to be painfully swollen, and the pyrexia of 101° to 102°F. was unaffected up to his admission.

Examination revealed an acutely ill, pale young male, obviously experiencing pain on motion of his knees. The oral temperature was 100.6°F., pulse 90, respirations 20. A moderate

injection of the conjunctivae with a dry exudate was present. No urethral discharge was detectable. The prostate gland was not abnormal. Both knee joints were swollen, of normal temperature and very painful on motion.

Laboratory examinations disclosed a normal urinalysis. The hemoglobin was 77 per cent, the red blood cell count was 3,560,000 and the white blood cell count was 8000. A sedimentation rate was 33 mm. per hour. X-rays of the knees and chest were not illuminating. Cultures of urine and synovial fluid obtained from the right knee joint failed to grow any bacterial organisms. Repeated electrocardiograms revealed variations in the size and direction of the T waves in leads I, III and V_5, suggestive of an active myocarditis. (Fig. 2.)

On May 3rd treatment with streptomycin 0.3 Gm. every three hours was instituted and continued for ten days. The conjunctivitis cleared promptly but he remained febrile for seven days. During the last three days of therapy a dramatic improvement in his joint swelling and pain occurred, with complete disappearance of the synovial fluid and he was granted a leave of absence to complete his collegiate examinations on May 14th.

Re-examination on June 4, 1947, demonstrated only minimal residual swelling in the left knee although he had been much more active than he had been instructed to be. The electrocardiogram revealed further increase in the deviations of the T waves from normal. The sedimentation rate was 23 mm. per hour. He was placed on a regimen of restricted activity and by June 21st the left knee appeared normal. The electrocardiogram had returned to normal. His anemia disappeared and the sedimentation rate had fallen to 8 mm. per hour. He was discharged from the hospital on June 22, 1947 and was well when last seen on February 18, 1948.

COMMENT

Etiology. Reiter[1] associated the disease with a spirochetosis but recent reports have failed to substantiate this concept. Later continental descriptions commented on the association of the syndrome with attacks of bacillary dysentery. Manson-Bahr[14] believes that the disease is the "familiar dysenteric polyarthritis." Recent letters and comments[17,18,20,21] from a series of physicians who had served in the Middle East during the war indicate that a similar syndrome was not uncommon as a late sequella of Shiga or Flexner dysentery. Short,[22] in an excellent discussion of arthritis occurring in the American Forces in the Mediterranean Theater, concluded that the syndrome triad occurring after bacillary dysentery and Reiter's syndrome were probably the same infection. Short further believed that the dysentery merely activated or provided a portal of entry for the etiologic agent, and that post-dysenteric arthritis was due to a secondary invader, not to the dysentery bacillus. In support of this hypothesis he advanced the facts that certain chemotherapies, while most effective in treatment of the dysentery, were ineffective in arthritis, that no Shigella group organisms had ever been recovered from joint fluids and that the pathologic findings of the synovia were consistent with those found in cases of non-dysenteric Reiter's syndrome. Others[19] believe that several types of the syndrome exist, one of which has a viral etiologic agent.

Dienes and Smith[23,30] were the first to suggest that a relationship might exist between certain types of arthritis, Reiter's syndrome and the pleuropneumonia-like organisms (L organisms). This group of organisms was first isolated from cattle by Nocard and Roux in 1898. Klieneberger renewed interest in them in 1935 by isolating numerous strains from rats infected with Streptobacillus moniliformis. Since that date Sabin[24] and many others have studied the various strains and the possible similarities between the polyarthritis produced by them in mice and human rheumatoid arthritis. Dienes[26,27] has described these organisms extensively and believes that they should be classified as bacteria in a separate group close to Hemophilus. They are not found commonly in the respiratory or gastrointestinal tract. Vallee[11] has discussed the above findings and others at length. Wallerstein, Vallee and Turner[25] have reviewed the possible relationship of the pleuropneumonia-like organisms to various types of arthritis and ulcerative colitis by

means of agglutinations of various serums against one strain of such organisms. Significant titers were found only in cases which had as presenting symptoms two of the three findings in the Reiter's triad. Lever and Crawford[3] attempted unsuccessfully to culture pleuropneumonia-like organisms from the secretions in one case. Dienes and Smith[30] reported four cases of Reiter's disease from whom positive cultures for L organisms were obtained from the prostatic fluids and two from synovial fluids.

The isolation of pleuropneumonia-like organisms from the urine and joint fluid of Case I when he was at the height of his first recurrence, and from the urine of Case II during the most severe period of his disease, strongly supports the suggestion of an etiologic relationship made by Dienes and Smith. The failure to repeat these findings after streptomycin treatment, or in a late, subsiding case, such as Case III, is not greatly disturbing. The inability to isolate the L organisms in Case IV, on the other hand, is unfortunate although signs of urinary tract infection were never present during our observation. Many investigators have noted that numerous strains of L organisms exist. This fact might help explain the variations in the severity and course of the syndrome and the variable ease of cultivation of them.

Our histories indicate that the channel of invasion was through the urogenital tract, contact having occurred by sexual intercourse. Symptoms appeared nine to sixteen days after exposure. Pyuria was a prominent finding. While Reiter's syndrome has not definitely been reported as occurring in females, the presence of pleuropneumonia-like organisms in the female genital tract has been frequently shown to occur in women with only mild or moderate gynecologic complaints.[23,28,29] The finding of an organism that apparently produces a severe systemic disease in males but only a local genitourinary infection in females is a most interesting one. Further studies on this observation might prove of value.

Cardiac Complications. Lever and Crawford's[3] first patient apparently died from some cardiac disorder but no autopsy was performed. Feiring[13] reported prolongation of the auricular-ventricular conduction in two cases. Our Case I presented a markedly prolonged P-R interval, with second degree heart block and inverted T waves in lead II, accompanied clinically by poor heart sounds. These findings suggested the presence of an acute myocarditis. Following treatment the electrocardiogram, heart rhythm and sounds became normal. Case IV presented no clinical cardiac abnormalities other than electrocardiographic T wave deviations in leads I, III and V_5. These became manifest only after treatment when the remainder of his clinical course had demonstrated vast improvement. Unfortunately, cardiac studies were not made in Cases II or III. These should be carried out on future patients as the present evidence is inadequate to determine the nature or extent of the myocardial damage.

Treatment. In the treatment of this syndrome nearly all available types of medication have been tried. Of these, fever therapy has been reported as successful by Strachstein[8] and Beiglbock.[14] Sargent[10] believed that typhoid vaccine was of benefit in the cases with eye complications. Neoarsphenamine, iodides, salicylates, sulfonamides and penicillin in turn have been used without striking effect. Gold salts have been used unsuccessfully by Baxter[20] and others. An analysis of forty-four cases recently reported in the American and British literature indicates that Reiter's syndrome is an infection presenting a variable course which may be short, long-standing or relapsing. Therefore, the effect of a given therapy, unless it is dramatic, is difficult to interpret. The analysis also indicates the average duration of a single attack of the syndrome to be four months. The minimum duration was twelve days and the maximum nine months. Recurrences were found in approximately 30 per cent of the cases, occurring from one to thirty months after the initial apparent recovery. Cases recurring

intermittently over eleven and fifteen years have been recorded.

We were led to try streptomycin* because of the earlier reports suggesting a relationship of the disease to organisms of the gram-negative bacillus variety. In addition, Dienes[26,27] and others had noted that certain variant forms of gram-negative organisms such as Streptobacillus moniliformis, conceivably susceptible to the antibiotic, were morphologically similar to the pleuropneumonia-like organisms. The organisms' classification near the susceptible group Hemophilus has been noted. No *in vitro* studies were made by us in respect to the effect of streptomycin on subcultures of the organisms obtained from the urine or synovial fluids. Our clinical experience, however, in the streptomycin treatment of chronic prostatitis due to infection with the L organisms had been so striking that we were anxious to try it in a possible systemic infection with the same organisms.

The daily dose of 4 Gm. of streptomycin for seven days was believed to give adequate concentration of the drug for a significant period of time. One patient treated with 2.5 Gm. per day for ten days did equally well. Longer treatment periods were not feasible because of the limited supply of the antibiotic. No reactions attributable to the drug were noted.

Our Case I had originally relapsed four months after apparent recovery from the initial attack which had been of eight months' duration. Following a week's therapy with streptomycin two and a half months of hospitalization were necessary for complete recovery, although fully half of this was required for the application of physiotherapy to the atrophied quadriceps femoris muscles. Eleven months after this he experienced what was probably a relapse. Re-treatment with streptomycin at that time effected a prompt recovery. No definite conclusions can be drawn from this. Case II was given a trial of other medication before instituting streptomycin. During this period some improvement had occurred, but a relapse with increase in severity of symptoms associated with the recovery of pleuropneumonia-like organisms in the urine culture suggested a trial of streptomycin. Within two weeks of the institution of this therapy, marked amelioration in fever, urinary and joint symptoms had occurred. This again may have been the natural course of what was a milder disease than was apparent clinically. He has remained well for a year since treatment. Case III experienced a dramatic improvement while on streptomycin, but unfortunately a positive L-organism culture had not been obtained and the case was already of three and one-half months' duration. The possibility that the infection was waning and that mere hospitalization alone might have been sufficient to produce the striking improvement must be considered. Case IV responded strikingly in regard to fever and joint swelling, but the electrocardiographic changes appeared during and were most marked after treatment.

In conclusion it must be recognized that the disease may run a prolonged and disabling course. Our patients treated with streptomycin were returned to full activity considerably sooner than the average of the recently reported cases. It cannot be denied that this may have been coincidental, nor is it certain that sufficient time has elapsed to be sure that other recurrences will not appear. There was, however, a consistent prompt improvement in the genitourinary symptoms and signs during or immediately after treatment. The lack of serious joint or eye complications in our four cases also seems more than fortuitous. The results are sufficiently promising to warrant the further use of this antibiotic in other cases of this syndrome.

* The author wishes to acknowledge the interest and cooperation of the Streptomycin Committee, Veterans Administration, Washington, D.C., which supplied the streptomycin.

SUMMARY

1. Four additional cases of Reiter's syndrome are presented. In two of these pleuropneumonia-like organisms were ob-

tained from the urine and in one from the knee effusion fluid. This is in accord with the previous findings of Dienes and Smith who have suggested that an etiologic relationship may exist between this group of organisms and the syndrome.

2. The electrocardiographic and cardiac abnormalities in two cases are noted, and previous observations regarding cardiac complications are briefly discussed.

3. Three patients were treated for seven days with a total daily dose of 4 Gm. of streptomycin; the fourth patient received 2.5 Gm. a day for ten days. The results were not conclusive but sufficiently encouraging to warrant further use of this therapy. No untoward effects of treatment appeared.

The author wishes to express his gratitude to Dr. Louis Dienes of the Massachusetts General Hospital for performing the cultures in Case 1 and for his generosity in instructing us in the technique of such cultures. The helpful suggestions of Drs. Marian Ropes and Walter Bauer of the same hospital are also gratefully acknowledged.

REFERENCES

1. Reiter, H. Ueber eine bisher unerkannte Spirochaeteninfektion (Spirochaetosis Arthritica). *Deutsche med. Wchnschr.*, 42: 1535, 1916.
2. Bauer, W. and Engleman, E. P. A syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's disease). *Tr. A. Am. Physicians*, 57: 307, 1942.
3. Lever, W. F. and Crawford, G. M. Keratosis blennorrhagica without gonorrhea (Reiter's disease?). *Arch. Dermat. & Syph.*, 49: 389, 1944.
4. Colby, F. H. Renal complications of Reiter's disease. *J. Urol.*, 52: 415, 1944.
5. Rosenblum, H. H. So-called Reiter's disease. *U. S. Nav. M. Bull.*, 44: 375, 1945.
6. Hollander, J. L., Fogarty, C. W., Jr., Abrams, N. R. and Kydd, D. M. Arthritis resembling Reiter's syndrome. Observations on 25 cases. *J. A. M. A.*, 129: 593, 1945.
7. Miller, C. D. and McIntyre, D. W. A syndrome termed Reiter's disease (urethritis, conjunctivitis and arthritis). *Ann. Int. Med.*, 23: 673, 1945.
8. Strachstein, A. Reiter's disease. Report of a case successfully treated. *New York State J. Med.*, 45: 2190, 1945.
9. Lucas, R. L. and Weiss, H. Gonorrheal syndrome without gonorrhea. Reiter's disease. *Arch. Ophth.*, 34: 97, 1945.
10. Sargent, J. C. Reiter's syndrome. *J. Urol.*, 54: 556, 1945.
11. Vallee, B. L. Reiter's disease. Review of the literature and report of a case. *Arch. Int. Med.*, 77: 295, 1946.
12. Twiss, J. R. and Douglas, A. H. R. Reiter's disease. Report of two cases. *Ann. Int. Med.*, 24: 1043, 1946.
13. Feiring, W. Reiter's disease with prolonged auriculo-ventricular conduction. *Ann. Int. Med.*, 25: 498, 1946.
14. Manson-Bahr, P. Abstract and discussion of article by Beiglbock. *Bull. War Med.*, 4: 653, 1944.
15. Jackson, W. P. U. The syndrome known as "Reiter's disease." *Brit. M. J.*, 2: 197, 1946.
16. Wrigley, F. Reiter's disease. *Brit. M. J.* 2: 199, 1946.
17. Herson, R. N., March, F. and Kay, J. Correspondence. *Brit. M. J.*, 2: 275, 1946.
18. Wood, P. and Kersley, G. D. Correspondence. *Brit. M. J.*, 2: 309, 1946.
19. Denfield, J. Correspondence. *Brit. M. J.*, 2: 555, 1946.
20. Baxter, C. R. Reiter's disease. *Brit. M. J.*, 2: 858, 1946.
21. Forbes, D. A case of Reiter's disease. *Brit. M. J.*, 2: 859, 1946.
22. Short, C. L. Arthritis in the Mediterranean Theatre of Operations. *New England J. Med.*, 236: 468, 1947.
23. Dienes, L. and Smith, W. E. Relationship of pleuropneumonia-like organisms to infections of human genital tract. *Proc. Soc. Exper. Biol. & Med.*, 50: 99, 1942.
24. Sabin, A. B. The filterable micro-organisms of the pleuropneumonia group. *Bact. Rev.*, 5: 331, 1941.
25. Wallerstein, R., Vallee, B. and Turner, L. Possible relationship of the pleuropneumonia-like organisms to Reiter's disease, rheumatoid arthritis and ulcerative colitis. *J. Infect. Dis.*, 79: 134, 1946.
26. Dienes, L. The significance of the large bodies and the development of L type of colonies in bacterial cultures. *J. Bact.*, 44: 37, 1942.
27. Dienes, L. Morphology and nature of the pleuropneumonia group of organisms. *J. Bact.*, 50: 441, 1945.
28. Klieneberger-Nobel, E. Pleuropneumonia-like organisms in the human vagina. *Lancet*, 2: 46, 1945.
29. Salaman, M. H., King, A. J., Bell, H. J. and Wilkinson, A. E. The isolation of organisms of the pleuropneumonia group from the genital tract of men and women. *J. Path. & Bact.*, 58: 31, 1946.
30. Dienes, L. and Smith, W. E. Studies of the incidence and pathogenicity of pleuropneumonia-like organisms in humans. *J. Clin. Investigation*, 25: 911, 1946.

Clinical Value of Examination of the Gastric Contents for Tubercle Bacilli*

ANDREW L. BANYAI, M.D.

Milwaukee, Wisconsin

To Meunier[1] belongs the credit for being the first to advocate and practice examination of the gastric contents for tubercle bacilli. This method, however, was not accepted for general diagnostic use until the publication of the studies of Armand-Delille and Vibert[2] in 1927. Since then a great deal of thought has been given to evaluation of this procedure. In patients with parenchymal pulmonary tuberculosis who do not expectorate or who have negative sputum, tubercle bacilli were found in the gastric contents in 60 per cent of the cases studied by Gad,[3] in 55 per cent of Gullbring and Levin's cases[4] and in about 20 per cent of the cases of Ulmar and Ornstein.[5] In children with pulmonary tuberculosis (parenchymal or hilar), Opitz[6] found tubercle bacilli in the gastric contents in 93 per cent, Boer[7] in 73 per cent and Langer[8] in 40 per cent. Gourley[9] examined 210 tuberculous children and found that the gastric contents were positive for tubercle bacilli by guinea pig inoculation in 40 per cent. An excellent review of the pertinent literature up to 1937 is available in her communication. The investigations of Stiehm[10] revealed the significant fact that 71.4 per cent of his patients with minimal pulmonary tuberculosis and negative sputum had gastric aspirations positive for tubercle bacilli. Roper and Ordway[11] reported that by the addition of gastric lavage to examinations of sputum, positive recovery of tubercle bacilli was doubled in newly admitted tuberculous patients. In a similar group of patients, Robinson and Dunn[12] found that 29 per cent of the individuals examined gave positive results by gastric lavage. The positive bacteriological findings varied according to the stage of the disease in their cases; 23 per cent positive in patients with minimal tuberculosis, 27.5 per cent in the moderately advanced and in 36 per cent in the far advanced groups. They recorded 32 per cent positive findings in the gastric contents of patients who had no expectoration.

I have been using gastric aspirations in my practice since 1933. During this period, the value of this procedure has become more and more evident. On the basis of my own experience as well as of others, I am convinced that bacteriological examination of the fasting gastric contents can be used to advantage in tuberculosis work for the following purposes: (1) In clinical diagnosis in institutional as well as in private practice; (2) for the management of tuberculous patients who are treated by bed rest or by some form of pulmonary relaxation therapy; (3) in follow-up examinations of patients who presumably recovered from tuberculosis; (4) for bacteriological screening of individuals who had close contact with persons suffering from tuberculosis, and (5) for the study of individuals who are found to have abnormal findings in their chest roentgenograms taken during mass surveys, whenever such lesions suggest the possibility of active tuberculosis.

Securing gastric specimens for bacterio-

* From the Department of Medicine, Marquette University Medical School, Milwaukee, Wisconsin.

logical examination is a simple procedure that can be performed by the physician, by a trained attendant or by a laboratory technician. It is preferable to aspirate the gastric contents rather than to wash out the stomach. Aspirations are done on five successive mornings as soon after rising as feasible. In Poulsen and Andersen's[13] investigation of 199 tuberculous children, tubercle bacilli were recovered from the gastric contents in 77 per cent on the first examination, in 96 per cent after the second examination, and in 100 per cent when five gastric specimens were examined. My findings are in harmony with these observations.

The fasting gastric contents are aspirated by means of a sterilized No. 16 French nasal catheter. Smaller tubes are used in children and in infants. The tube is passed through the nose readily if its tip is moistened with sterile glycerine. It can easily be maneuvered through the nasal cavity, even in the presence of minor submucous bony deformities or of septal deviations. As soon as the tip reaches the pharynx, the patient is instructed to swallow repeatedly while the tube is passed down the esophagus. There is very little discomfort from this procedure and the patients readily accept repeated gastric aspirations. By means of a 10-cc. or 20-cc. glass syringe, the gastric contents are removed and are collected in a sterile container.

For some years, it has been the routine in my practice to pool individual gastric specimens obtained on successive days. The pooled specimens were prepared for culture or animal inoculation as a single specimen. This was done with the assumption (1) that the end results are better than when examining individual samples separately, and (2) that keeping the gastric contents in the refrigerator until all specimens of the series are collected does not influence the outcome of the examination unfavorably.

Recently, however, considerable doubt has arisen concerning the soundness of this practice in view of the possible harmful effect of the human gastric juice upon the tubercle bacilli. The first report dealing with the latter subject was published by Falk.[14] He observed that tubercle bacilli remained viable and virulent in spite of their exposure to gastric juice. Similar observations were made by Cadeac and Bourney[15] in their feeding experiments on dogs. They noted the survival of virulent tubercle bacilli twelve hours after feeding to animals in food mixtures. More recent and more accurate research studies relative to this question, however, brought out contrary results. The work of Floyd and Page[16] is of particular interest in this respect. They added a suspension of virulent tubercle bacilli to 15 cc. of artificial gastric juice and incubated it at body temperature for three-, six- and twelve-hour periods. Following incubation, the mixture was neutralized and inoculated into guinea pigs. The experimental animals developed tuberculosis the extent and severity of which was more or less proportionate to the length of exposure of the tubercle bacilli to the gastric juice. The tuberculous lesions in the six-hour group were about one-half of those found in the group inoculated with tubercle bacilli after three-hour digestion with gastric juice. The lesions were nearly 80 per cent less in the twelve-hour group than in animals inoculated with the three-hour specimen. Corroborative pertinent findings were noted by Kramer[17] in his investigations. He mixed 40 cc. of normal human gastric juice with 5 cc. of sputum of tuberculous patients and kept the mixture incubated at body temperature. The mixture was shaken from time to time so as to simulate the motion of the stomach. Guinea pigs were inoculated with 2 cc. of this mixture after incubating for one, four, ten, twenty-one, forty-five and sixty-eight hours. Two and a half months after inoculation, the animals

were sacrificed and anatomical, histological and bacteriological examinations were carried out. It was observed that tubercle bacilli present in the sputum began to lose their pathogenicity in ten hours. After twenty-one hours, their capacity to induce tuberculosis in guinea pigs was entirely lost. The loss of virulence of the tubercle bacillus is not due to hydrochloric acid. Inkster and Gloyne[18] observed that mixing sputum positive for tubercle bacilli with gastric juice of high acidity (62 degrees) did not destroy the virulence of these micro-organisms. Roper and Ordway[11] demonstrated that the viability of human tubercle bacilli was not affected by free hydrochloric acid up to tenth-normal strength even after forty hours of exposure (the normal fasting stomach usually contains free hydrochloric acid in concentrations less than twentieth-normal). In view of these findings, it is advisable not to pool specimens suspected of containing tubercle bacilli. Instead, the aspirated gastric contents should be examined individually as soon as possible after removal from the stomach.

The technic of preparing gastric specimens for culture has been used in the overwhelming majority of my cases. Experience has shown that tubercle bacilli are detectable by this method as reliably as by animal inoculation. This observation is in harmony with the experimental studies of Corper.[19] He proved nearly twenty years ago that the culture method was as efficient as guinea pig inoculation for the detection of tubercle bacilli. Corper pointed out the added advantage of the culture method in that the growth of tubercle bacilli on culture medium is not affected by the virulence of the micro-organism. At the same time, in contrast to animal inoculation, one does not have to reckon with the possible natural resistance of the animal body. It is a well known fact that tubercle bacilli of lowered virulence may not produce tuberculosis in the guinea pig. The culture method is, of course, simpler and less expensive. On very rare occasions, one may find non-pathogenic acid-fast bacilli in the gastric contents. These can be identified readily by their morphological, tinctorial and colonial characteristics, and, in case of doubt, by guinea pig inoculation. Claims for the usefulness of cultures are put forward with the full realization that in some instances it is extremely difficult or impossible to grow tubercle bacilli from the aspirated gastric contents. Occasional failure of this procedure is not to be attributed to anything but to unavoidable technical limitations or perhaps, to the lowered viability of the micro-organisms.

Since the time I began to resort to bacteriological examination of the gastric contents, it became obvious that the concentration method is unreliable. Even more unreliable is examination of a simple smear. To illustrate this point, it may be mentioned that of 783 gastric specimens positive for tubercle bacilli by culture there were only 147 positive by the concentration method (18.7 per cent) and only sixty-eight were positive on simple smear (8.6 per cent). Simultaneous examination of a gastric specimen by culture and guinea pig inoculation does not always give identical results. Discrepancies between these two methods have been noted on repeated occasions. From the same material, culture may give positive results while guinea pig inoculation reveals no evidence of tuberculosis, and vice versa. The explanation of such differences should be sought in the following possible factors: (1) The tubercle bacilli in the specimen are so attenuated that they are incapable of infecting a guinea pig, or they lose their viability during the process of preparation for the culture. (2) There may be so few tubercle bacilli present in the gastric specimen that the portion of the gastric sample used for culture or animal inoculation does not contain micro-organisms. As

is well known, a similar situation often arises when two guinea pigs are inoculated with the same material at the same time. (3) Using more centrifuged sediment for one test than for the other may lead to contradictory results.

The technic of preparing cultures from gastric specimens, as previously reported by Anderson,[20] is as follows: Enough potassium hydroxide solution is mixed with the material to make a concentration of 1.5 per cent hydroxide, and the mixture is kept at 40°c. for thirty minutes or long enough to become warm. The liquefied specimen is centrifuged at high speed for twenty minutes, decanted and resuspended in a few cc. of physiological saline solution. A drop of brom-cresol-purple solution is added before neutralizing with 5 per cent hydrochloric acid. By pouring off the fluid before the addition of acid, one avoids reprecipitation of the protein. Keeping the solids finely divided results in a more evenly distributed culture. The neutral residue is washed and centrifuged in about 40 cc. of physiological saline solution; after this, it is ready for culture. As a rule, the entire sediment is used for this purpose, dividing it among three slants of a modified Petragnani's medium in oval test tubes measuring 155 by 27 by 17 mm. The tubes are incubated in a nearly horizontal position until no moisture is visible on the surface of the medium (usually forty-eight hours). The tubes are then sealed with a mixture of two parts of paraffin to one part of vaseline, and incubated in the upright position until evidence of bacterial growth is noted, or for a maximum period of eight weeks. The cultures are examined grossly every week. When macroscopic growth appears, smears are prepared for examination on any first growth and as often thereafter as necessary for establishing accurate identification of the micro-organism. Preparations from cultures are best stained individually so as to avoid possible contamination of negative slides in the same batch. Alcoholic solution of carbol fuchsin, with a few crystals of pure sodium chloride sprinkled over the dye, is preferable to steaming over flame. It is common to find only one culture medium out of three with bacterial growth. Usually, fewer than five colonies are seen, although colonies numbering between five and ten, or even more, may occur. Whenever the cultural growth, as observed grossly or microscopically, appears to vary from usual, it is tested by subculturing to ascertain whether or not the micro-organisms grow at room temperature or have the ability to grow in the incubator in a shorter period of time than that required by the tubercle bacillus. The earliest positive colonies appear in about sixteen days. The largest number are noticeable between the twentieth and twenty-third day. Approximately 90 per cent of the positive cultures are reportable by the end of the fifth week. The average length of time required for positive culture is twenty-five days.

Concerning the origin of tubercle bacilli found in the fasting gastric contents, the following points deserve consideration:

1. The ingestion of tubercle bacilli can be excluded with reasonable certainty because the patient is not permitted to take nourishment during the night and morning preceding the gastric aspiration. Furthermore, it is unlikely that viable bacilli will be found in milk from tuberculin-negative herds (tuberculosis in cattle has been virtually eradicated throughout the United States) or in milk which has been pasteurized.

2. The question might arise as to the likelihood of finding tubercle bacilli in healthy individuals who have been exposed to tuberculosis incidentally or professionally (physicians, nurses and hospital and sanatorium attendants). It has been my experience, and this coincides with the observations of others, that tubercle bacilli are never

found in the fasting gastric juice of healthy persons or of those with non-tuberculous pulmonary diseases.

3. Clinically manifest tuberculosis of the tonsils as a source of tubercle bacilli in the aspirated stomach contents is extremely rare, even in patients with long-standing, far advanced pulmonary tuberculosis. According to Rather,[21] microscopic examination revealed active tonsillar tuberculosis only thirty-five times in 19,000 tonsillectomies. This is equivalent to 0.18 per cent, a percentage which is much lower than the incidence of significant reinfection tuberculosis of the lung currently found in mass roentgenological surveys in this country.

4. The rôle of tuberculosis of the stomach as a source of tubercle bacilli is insignificant. In a series of 1,043 necropsies of tuberculous patients, Cullen[22] noted tuberculosis of the stomach in four cases (0.38 per cent). A similar study by Kabuki[23] revealed only a 0.11 per cent incidence of gastric tuberculosis, while Browne and his associates[24] reported thirty cases out of a group of 1,321 necropsies in patients who died of tuberculosis (0.22 per cent). In a series of 10,000 postmortem examinations, Collinson and Stewart[25] found only three cases of gastric tuberculosis (0.03 per cent). Gentile[26] reports a collective review of Mirolli,[27] covering postmortem findings in 71,871 cases, which showed an incidence of 0.21 per cent. Sullivan, Francona and Kirshbaum[28] recorded only two cases of tuberculosis of the stomach in 11,480 postmortem examinations (0.01 per cent). In both of these cases, evidence of active tuberculosis was found in the lungs. They found no gastric tuberculosis in necropsies of more than 10,000 non-tuberculous individuals. Also, they report that during the period from 1929 to 1938 only one case of tuberculosis of the stomach was encountered in 75,000 surgical specimens.

5. Regurgitation of tubercle bacilli-bearing intestinal juices into the stomach in case of intestinal tuberculosis is unlikely. Duodenal tuberculosis is exceptionally rare. Moreover, tubercle bacilli are easily demonstrable in the sputum of patients whose pulmonary tuberculosis is complicated by intestinal tuberculosis.

6. There is a very rare possibility of finding tubercle bacilli in the stomach as the result of perforation of a tuberculous mediastinal lymph node into the esophagus.

7. Tuberculosis of the nasopharynx in persons who have no demonstrable pulmonary tuberculosis is extremely rare and therefore has no clinical significance in this respect.

Possible sources of tubercle bacilli in the fasting gastric contents are as follows:

1. Frank tuberculous infiltration of the lung parenchyma, of the reinfection type or primary type, readily demonstrable on physical examination or roentgenogram.

2. Tuberculous hilar lymph nodes, which always signify a previous coexistent primary or reinfection-type lesion in the lung parenchyma, may discharge tubercle bacilli into the adjacent bronchi.

3. Active tuberculous lesions of the lung parenchyma, or tuberculous lymph nodes which may appear well fibrosed or calcified in the roentgenogram.

4. Active tuberculous foci in the lung or lymph nodes, which are not visualized on a standard postero-anterior roentgenogram of the chest, may be sources of tubercle bacilli found in the stomach. The difficulty in visualizing these lesions is due to the fact that they are localized in areas obscured by the heart shadow, the mediastinal structures, the dome of the diaphragm or by the bone structures of the thoracic cage.

5. Tubercle bacilli may originate from hidden or manifest tuberculous involvement of the bronchi and bronchioles, with or without secondary bronchiectasis.

6. Tubercle bacilli may originate from

lesions in the lung which cannot be visualized roentgenologically because their consistency is such that they do not cast a shadow when exposed to roentgen rays.

7. Minute lesions may be sources of tubercle bacilli. These lesions may not be observed roentgenologically either because of their small size or because of the absence of perifocal inflammation and edema.

With these considerations in mind, the following pointers are offered as possibly serviceable guides in every-day practice:

1. Assaying a pulmonary lesion from the diagnostic standpoint is a composite task and proper evaluation of the relevant components is of utmost importance. The diagnostic value of roentgenological findings should not be overestimated. The well known roentgenological similarity of various etiologically unrelated diseases supports this attitude. Grave errors may be committed when the diagnosis is based on the roentgenological appearance alone without due regard to other clinical and laboratory data. Although interpretation of the x-ray shadows is an important adjunct in this work, it is not nearly as essential as the bacteriological identification of the disease.

2. Examination of the fasting gastric contents for tubercle bacilli is indispensable, regardless of the apparent stage and extent of the disease, if the tuberculous patient does not expectorate or if the sputum is not acceptable for competent examination. Of course, there is more frequent need for gastric aspirations in minimal cases than in patients with far advanced pulmonary tuberculosis. But I have recorded the absence of cough and expectoration many times in patients in whom the diagnosis of far advanced tuberculosis was established beyond the shadow of a doubt. Unquestionably, similar observations have been made by others who have the opportunity to scrutinize the pulmonary status of a large number of individuals. As an example, I may refer to one of my patients seen recently. He was a white man, aged forty-nine years, who was ailing for several months with fever, night sweats, malaise and loss of weight. The family history was non-contributory and the past history was irrelevant. His temperature was 101.8°F. The physical findings were of no significance except with respect to the chest. Here there were signs of pulmonary infiltration over the upper two-thirds of the right lung and over the lower one-half of the left lung. The roentgenogram of the chest revealed the following findings: Right side: uniform pleural thickening with an underlying exudative process throughout, with a large cavity in the middle one-third. Left side: exudative lesion limited to the lower two-thirds. The patient had no expectoration. The diagnosis was established on the basis of gastric aspirations which revealed the presence of tubercle bacilli.

3. The number of gastric aspirations indicated is determined by the reasonableness of the suspicion of tuberculosis and varies from five to as high as fifteen. The greater the weight of circumstantial evidence, the greater should be the number of gastric aspirations. Points which should prompt a thorough bacteriological survey include: (1) History of exposure to a known case of tuberculosis; (2) previous pleurisy with effusion. It is estimated that 75 per cent of so-called idiopathic pleural effusions are tuberculous in origin and that approximately 50 per cent of the patients with this condition develop manifest pulmonary tuberculosis subsequently. (3) Pulmonary hemorrhage some time prior to the presenting illness; (4) extrapulmonary forms of tuberculosis in the past; (5) history of ischiorectal fistula; (6) chronic malnutrition; (7) silicosis; (8) asbestosis; etc.

4. Roentgenological findings do not always serve as reliable guides to the course of the tuberculous process. Often the lesion

may appear fibrosed or apparently calcified, remain stationary and suggest complete healing. Bacteriological examination of the fasting gastric contents, however, may reveal tubercle bacilli in some of these cases. This brings to mind the saying so often appropriate in the management of pulmonary tuberculosis, namely, "treat the patient and not the x-ray shadow." In such instances one should insist on periodically repeated examinations of the fasting gastric contents until it is found that they are consistently negative for tubercle bacilli. This is mandatory for the sake of the patient as well as for the sake of his environment. If this principle is disregarded, the patient may be released as cured when actually he is still suffering from active tuberculosis. Individuals who subsequently come in close contact with him will be exposed to the danger of infection with tubercle bacilli. In other words, a patient of this type becomes an unrecognized or unadmitted tuberculosis carrier.

5. During the course of certain artificial relaxation therapy measures, the interpretative inspection of the diseased lung, with the aid x-ray is virtually without value or it is a technical impossibility. Measures such as artificial pneumothorax, thoracoplasty, extrapleural pneumothorax, paraffin plombage and oleothorax induce a degree of pulmonary relaxation which *a priori* obscures the lung field where the lesion is localized. It may either be impossible or impracticable to attempt to re-expand the relaxed lung. A competent assessment of pathological changes, of their progression or retrogression cannot be made by visual means. At the same time, in consequence of the relaxation therapy, the patient ceases to cough or is not raising sputum satisfactory for bacteriological examination. The search for tubercle bacilli in the gastric contents is the only means at our disposal in such instances with which to gauge the recovery of the patient. When dealing with this problem, due consideration must be given to the rate of healing of the tuberculous process. It may take a period of one to two years before a patient with previously positive gastric specimens becomes negative for tubercle bacilli by this method. As an example, I may mention a patient of mine, a young woman with far advanced pulmonary tuberculosis who was treated by thoracoplasty. At completion of the procedure her sputum was positive for tubercle bacilli. Three months later, the sputum was negative but the subsequently examined gastric contents revealed the presence of tubercle bacilli. The patient became consistently negative when examined by gastric culture after the eighth month postoperatively. Altogether, this patient had fifteen examintions of gastric aspirations for tubercle bacilli, two months apart, following thoracoplasty and before she was classified as an apparently arrested case of tuberculosis.

6. The interval between gastric aspirations depends upon the character of the disease, the type of treatment applied, symptomatic and semeiological responses to treatment, and on objective findings noted on periodic examinations. It is well to bear in mind the limitations of small numbers of examinations. A pertinent case is that of a twenty-two year old patient of mine with minimal pulmonary tuberculosis and positive sputum. On strict bed rest, the sputum was converted to negative in four months. At this time, the gastric contents were also negative for tubercle bacilli. In spite of this, on the basis of an individual evaluation of this case, the patient was considered still to have active tuberculosis. For this reason, his rest regimen was continued. Our clinical judgment was vindicated subsequently when examination of the stomach contents three months later showed the presence of tubercle bacilli. Only when two additional sets of five gastric specimens were

found negative, two months and four months later, respectively, was the patient considered an apparently arrested case of pulmonary tuberculosis.

7. During the course of treatment of a tuberculous patient, the significance of the result of a single examination of the gastric contents must be interpreted with a great deal of caution and circumspection. This warning is offered on the basis of the experience that, not infrequently, a sample aspirated from the stomach may prove negative for tubercle bacilli while one taken the next day is positive. The acceptance of a single negative report as conclusive is bound to invite regrettable consequences. As an illustration, I wish to give the salient data from the record of one of my patients. She had moderately advanced pulmonary tuberculosis, with limited disease in each lung. At the time of her admission, the first gastric specimen was positive but the gastric contents obtained the next day were negative. Following three months of strict bed rest, converse findings were recorded on two successive days. Two and a half months later, a similar notation was recorded. At this time artificial pneumothorax was instituted on the more involved side. After six months' pneumothorax treatment, examination of the gastric contents was negative. However, tubercle bacilli were recovered from the aspirated material obtained on the following day. In view of past experiences, it was deemed advisable to carry on with pneumothorax treatment. This decision was followed by finding two negative gastric specimens three months later and a positive specimen two months thereafter. At this time, in view of roentgenologically demonstrable honeycomb cavitation in the lung opposite to the pneumothorax side, an extrapleural paraffin pneumonolysis was done to obliterate these cavities. The patient was kept on a rest regimen and on graded exercise for an additional twelve months. During this period, she had fifteen gastric aspirations (three series of five each). All these having been negative, the patient was classified as an apparently arrested case of pulmonary tuberculosis.

8. Examination of the gastric contents may serve as a useful index in determining the patient's exercise tolerance following prolonged bed rest or major thoracic surgery. It is a matter of common knowledge that minute changes resulting from a flare-up of a tuberculous process may not be visualized on the roentgenogram and may easily escape detection on physical examination. Also, it is known that certain forms of reactivation or progression of the disease may cause no symptoms whatever. In the past, because of these limitations in our ability to assay the patient's condition, many disastrous errors in judgment were committed by permitting too early or too much exercise. In gastric aspirations we have a reliable and sensitive means at our disposal for regulating the patient's activities and for ascertaining reactivation of the disease long before it becomes visible on the x-ray film.

9. The bacteriological examination of the fasting gastric contents is far superior to the erythrocyte sedimentation test in ascertaining whether a tuberculous process in the lung is active or healed. All in all, it is my impression that the clinical value of the erythrocyte sedimentation test in tuberculosis is greatly overestimated. A study of the sedimentation rate of the red blood cells in approximately 10,000 tuberculous patients seen in my practice revealed that 8 per cent of them had normal values. Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in those with a reinfection type of the disease. The erythrocyte sedimentation rate does not parallel the type and extent of tuberculosis.

Normal rates were encountered in association with minimal, moderately advanced and far advanced infection, with productive and with exudative pulmonary tuberculosis and with solitary and multiple cavities. The size of the pulmonary cavities varied from honeycombing to cavities 45 mm. by 70 mm. in diameter. Aspirated gastric contents positive for tubercle bacilli were encountered in association with normal sedimentation rates on frequent occasions.

10. I have called attention, in previous communications,[29] to the importance of bacteriological examination of the fasting gastric contents in extrapulmonary forms of tuberculosis. In a group of twenty-two patients with bone and joint tuberculosis, without demonstrable active tuberculous involvement in the lung, tubercle bacilli were found in the stomach juice in seven (31.8 per cent). This rather surprising finding was amplified by investigating the usefulness of this method in other extrapulmonary manifestations of this disease. These included tuberculous lymphadenitis, pleurisy with effusion, renal tuberculosis and lupus vulgaris. The results show that examination of the fasting gastric contents is of importance in establishing the diagnosis in a substantial percentage of such cases.

CONCLUSIONS

1. Bacteriological examination of the fasting gastric contents is an important, sensitive and reliable aid in the diagnosis of tuberculosis. It is a simple procedure which can be carried out by the physician, by a trained nurse, attendant or laboratory technician.

2. It is useful not only in pulmonary tuberculosis but also in extrapulmonary forms of this disease.

3. It is of value as a gauge in the clinical management of tuberculous patients in that, with its aid, one can ascertain the progress of the healing process in pulmonary cases undergoing any form of medical or surgical treatment.

REFERENCES

1. Meunier, H. Bacteriological examination of the gastric contents in the diagnosis of pulmonary tuberculosis in children. *Presse méd.*, 2: 81, 1898.
2. Armand-Delille, P. F. and Vibert, J. Bacteriological diagnosis of pulmonary tuberculosis in infants by the examination of the stomach contents. *Presse méd.*, 35: 402, 1927.
3. Gad, U. On the diagnostic value of gastric lavage in adult patients without roentgenographic foci in the lungs. *Acta tuberc. Scandinav.*, 11: 189, 1937.
4. Gullbring, A. and Levin, N. Importance of gastric lavage for the demonstration of tubercle bacilli in adults with pulmonary tuberculosis. *Acta med. Scandinav.*, 93: 168, 1937.
5. Ulmar, D. and Ornstein, G. G. Gastric examination in pulmonary tuberculosis with negative sputum. *J. A. M. A.*, 101: 835, 1933.
6. Opitz, H. Surprising findings of tubercle bacilli in young children. *München. med. Wchnschr.*, 78: 949, 1931. Idem. Detection of tubercle bacilli in apparently healthy children and in closed childhood tuberculosis. *Med. Welt*, 5: 1239, 1931. Idem. Actual frequency of open tuberculosis in children. *Beitr. z. klin. d. Tuberk.*, 82: 296, 1933.
7. Boer, H. D. Open tuberculosis in children. *Maandschr. v. kindergeneesk.*, 1: 377, 1932.
8. Langer, H. Practical consequences of detection of tubercle bacilli in symptom-free children. Quoted by Dietzel, K. Infectiousness of active tuberculosis of the bronchial lymph nodes. *Ztschr. f. Tuberk.*, 80: 359, 1938.
9. Gourley, I. Search for tubercle bacilli in the gastric contents of tuberculous and nontuberculous children. *Tr. Nat. Tuberc. A.*, 33: 131, 1937.
10. Stiehm, R. H. Tubercle bacilli in the gastric contents—An important diagnostic and prognostic finding, *Am. J. M. Sc.* 194: 340, 1937.
11. Roper, W. H. and Ordway, W. H. Gastric lavage in adults with pulmonary tuberculosis. *Am. Rev. Tuberc.*, 43: 543, 1941.
12. Robinson, J. L. and Dunn, W. T. Gastric lavage and sputum cultures. *Am. Rev. Tuberc.*, 47: 413, 1943.
13. Poulsen, V. and Andersen, A. O. Demonstration of tubercle bacilli and significance in prognosis, therapy and estimation of danger of infection. *Am. J. Dis. Child.*, 47: 307, 1934.
14. Falk. Fate of infectious agents in the gastrointestinal tract. *Arch. Path. Anat. u. Physiol.*, 93: 177, 1882.
15. Cadeac and Bourney. The bactericidal role of the digestive juices. *La Province Med.*, 8: 324, 1893.
16. Floyd, C. and Page, C. G. The action of artificial gastric juice and duodenal secretions on tubercle bacilli. *Am. Rev. Tuberc.*, 48: 174, 1943.
17. Kramer, C. H. Effect of human gastric juice on tubercle bacilli. *Am. Rev. Tuberc.*, 53: 385, 1946.
18. Inkster, J. and Gloyne, S. R. The bactericidal action of gastric juice on B. tuberculosis. *Brit. M. J.*, 2: 1024, 1921.
19. Corper, H. J. The certified diagnosis of tuberculosis. *J. A. M. A.*, 91: 371, 1928.

20. Anderson, S. V. Gastric aspiration culture and the control of tuberculosis. *Am. J. M. Technology*, 2: 161, 1945.
21. Rather, L. J. Tuberculosis of the tonsils. *Am. J. Path.*, 19: 725, 1943.
22. Cullen. Quoted by Flexner, J. and Baum, O. Gastroscopic observations in pulmonary tuberculosis. *Am. J. M. Sc.*, 204: 101, 1942.
23. Kabuki, Y. An operated case of gastric tuberculosis. *Deutsche Ztschr. f. Chir.*, 355: 309, 1942
24. Browne, D. C., McHardy, G. and Wilen, C. Gastric mucosal changes in tuberculosis. *Am. J. Digest. Dis.*, 9: 407, 1942.
25. Collinson, H. and Stewart, M. J. Chronic peptic ulcer of the stomach with acute miliary tuberculosis of the gastric mucosa. *Brit. J. Surg.*, 15: 626, 1928.
26. Gentile, G. Surgical observations on tuberculosis of the stomach. *Arch. ital. di chir.*, 48: 629, 1938.
27. Mirolli, A. Contributions to the study of tuberculosis of the stomach. *Arch. ital. di chir.*, 24: 83, 1929.
28. Sullivan, R., Francona, N. and Kirschbaum, J. Tuberculosis of the stomach. *Ann. Surg.*, 112: 225, 1940.
29. Banyai, A. L. and Cadden, A. V. Bacteriological examination of the gastric contents in the diagnosis and management of tuberculosis of the bones and joints. *J. Bone & Joint Surg.*, 28: 137, 1946. Banyai, A. L. Tubercle bacilli in the stomach contents—An important diagnostic finding in extrapulmonary forms of tuberculosis. Paper presented at the annual meeting of the American Academy of Tuberculosis Physicians, San Francisco, California, June 30, 1946.

Technical Aspects of Therapeutic Malaria*

LAWRENCE I. KAPLAN, M.D. *and* HILTON S. READ, M.D.
New York, New York *Atlantic City, New Jersey*

THE technical aspects of induced malaria in the treatment of neurosyphilis have been inadequately appreciated, even in many institutions concerned with its use at the present time. Overburdened by the effort to provide sufficient neuropsychiatric care many of these hospitals have lacked the opportunities and facilities for studying the technical problems involved in this therapeutic procedure. Reliance upon the arbitrary, time-worn use of routine inocula of 5 to 10 cc. of infected blood, with lack of attention to immune mechanisms involved in the use of different malaria strains, among other things, has resulted in irregular, unpredictable infections, often difficult to evaluate with respect to therapeutic adequacy.

Success of penicillin in the treatment of neurosyphilis has by no means outmoded the usefulness of inoculation malaria in this disease. Reports of results following penicillin therapy alone[1,2] certainly emphasize its value in this frequently crippling affliction, but certain types of neurosyphilis, notably those involving the parenchymatous central nervous system, will probably require a combination of induced malaria (as the most valuable form of fever therapy) and penicillin (as the most desirable chemotherapeutic agent). In the light of experience in the armed forces it therefore seems appropriate at this time to recount recent advances in the technical aspects of therapeutic malaria and their practical applications.

In the interval between July, 1944 and October, 1945, a total of more than 450 patients with neurosyphilis were treated with induced malaria at the Finney General Hospital Neurosyphilis Center. Every clinical variety of neurosyphilis was encountered but the majority of cases were of the asymptomatic type in young, otherwise healthy, male adults. The course of therapeutic malaria and its complications could be readily evaluated, therefore, without the confusing introduction of neuropsychiatric symptomatology. Nine strains of plasmodia were utilized for inoculations. These consisted of five strains of Plasmodium vivax, four of which were recovered from individuals originally infected with the natural disease in the Southwest Pacific theatre, three strains of Plasmodium malariae and one strain of Plasmodium falciparum. Technics of inoculation included application of infected mosquitoes and the intravenous or intradermal inoculation of infected blood.

The technical advances in the use of therapeutic malaria can be roughly divided into three phases, each of which will be considered separately, as follows:

QUANTITATIVE PARASITE COUNT

Estimation of the density of malaria parasites in the blood of an infected individual has contributed greatly to better understanding of the characteristics of both natural and induced malarial infections. With the aid of this laboratory procedure, the immune response can be more precisely recognized and classified, and the technics of blood inoculation for inducing the therapeutic disease can be placed on a predictable, quantitative basis.

Technic. The technic of the quantitative parasite count, Boyd's modification of that described by Earle and Perez[3] may be de-

* Investigations reported in this paper were carried out at the Army's Neurosyphilis Center, Finney General Hospital, Thomasville, Ga., in collaboration with Mark F. Boyd, M.D., Director of the Station for Malaria Research (Rockefeller Foundation) Tallahassee, Fla., and Frederic T. Becker, M.D., former Chief of Dermatology and Syphilology Section, Finney General Hospital.

scribed as follows: The materials required are (1) capillary pipettes graduated to deliver 5.0 c. mm. of blood; (2) glass slides on which are ruled or etched rectangles measuring 3.0 by 15.0 mm.; (3) a microscope, the ocular of which contains a Howard disc micrometer, the surface of which is ruled with one large square, divided into sixteen minor squares and so calibrated that with a predetermined tube length the area on a slide covered by the large square on the micrometer is known; (4) diluted Giemsa's stain.

The method used is as follows: (1) Discharge exactly 5.0 c. mm. of blood onto the ruled rectangle of the slide carefully avoiding bubbles. With a needle point carefully spread the blood out to the edges and into the corners of the ruled area. Allow it to stand in a horizontal position until dry. Since 5.0 c. mm. of blood are spread over 45 sq. mm., there will be spread over each sq. mm. of the rectangle 0.11 c. mm., or 1/9 c. mm. of blood. (2) Stain smear in Giemsa's stain as any other thick smear; wash, drain and dry. (3) If it is assumed that calibration of the micrometer disc has shown that the outline of the large square covers 0.01 of a sq. mm. on a slide when the stained smear is placed under the microscope, it will be necessary to count the parasites observed in one hundred consecutive and discrete fields to obtain a sample of the parasites in the blood spread over 1.0 sq. mm. The fields should be selected while the smear is transversed on different parallel lines. The total of the parasites counted in one hundred fields will, when multiplied by nine, give the number/cu. mm. (Fig. 1.)

Classification and Management of Immune Responses. Normal variations in the parasite density for malaria infections differ with the species of plasmodia encountered. Vivax parasitemias usually average 20 to 40,000 parasites per c. mm. at the height of activity and rarely exceed 50,000 per c. mm. Quartan (P. malariae) parasitemias, involving chiefly the aged erythrocytes, rarely reach a height of 20,000 per c. mm. and usually remain

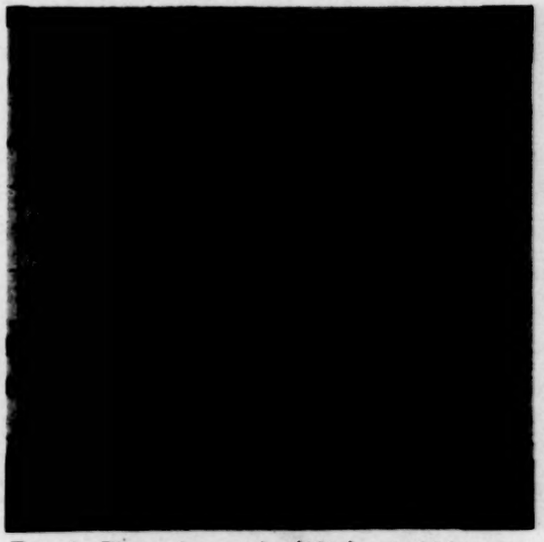


FIG. 1. Photomicrograph (95×) of thick smear, showing malaria parasites in relation to the squares of the Howard disc.

below 10,000 per c. mm. There is no established limit to falciparum parasitemias but the danger line averages between 100 and 200,000 parasites per c. mm. If a falciparum parasitemia exceeds 500,000, a fatality is almost inevitable unless prompt, repeated phlebotomies and transfusions are successfully instituted.

Correlation of hourly temperature records and quantitative daily parasite counts in a series of 300 cases of neurosyphilis (225 white and 75 negro patients) treated with therapeutic malaria has demonstrated four main types of immunologic reactions:[4] (1) hyperimmune; (2) immune; (3) partially immune; (4) hypersusceptible.

In the hyperimmune response, rarely encountered in therapeutic malaria, neither temperature elevation nor demonstrable parasitemia follows inoculation of massive doses of trophozoites (50 to 100 million). Presumably these patients have had previous exposure to the same strain of malaria or have a marked racial immunity, both of a homologous type.

The immune reaction is characterized by development of a slight parasitemia following heavy inoculation, unaccompanied by any febrile response above 100°F. This was frequently encountered in negro soldiers inoculated with a vivax strain. When

it occurs in white patients, it usually serves as evidence that they have had previous exposure to a homologous strain of malaria.

The partially immune response (Fig. 2) has been a provoking problem in therapeutic malaria. It initiated the cross inoculation immunity studies, an effort to find practical means of completing therapeutic malaria courses without prohibitively prolonged periods of hospitalization. This type of immune response can often be predicted by merely eliciting from the individual the history of a previous attack of natural malaria. However, a number of white patients with negative histories are still subject to a partially immune response.

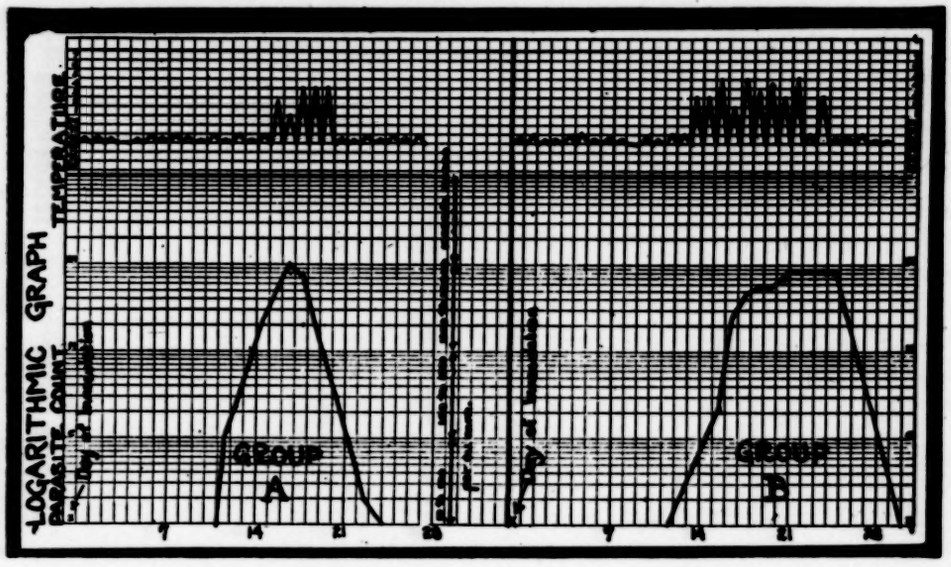


FIG. 2. The partially-immune response, Groups A and B, illustrating the relation of the parasite density to the febrile course.

In these cases following inoculation parasites will appear in the blood and slowly increase to a density of several hundred per c. mm. before the occurrence of any febrile response. The patient then experiences from three to seven paroxysms whereupon the parasite count drops precipitously and the patient becomes afebrile. Individuals developing partially immune responses may be divided into two groups: (A) Those experiencing less than five paroxysms of fever to 103°F. or more and (B) those experiencing five to eight such episodes. This type of reaction, particularly group B, indicates that the patient has had previous experience with a heterologous strain of malaria and will not complete a successful treatment course with the single inoculation. Those who in spite of thorough interrogation evade pre-inoculation recognition should be discovered promptly postinoculation by the course of the parasitemia, and should be treated with a plasmodicidal drug and reinoculated with another strain or species of malaria.

The hypersusceptible patient (Fig. 3) will usually develop fever several days before parasites are microscopically discernible in the blood. With the parasitemia maintained at a high level, these individuals may experience a prolonged number of paroxysms unless interrupted by antimalarial therapy. These courses usually average sixteen to twenty-five paroxysms but a total of twenty-seven paroxysms was permitted in one of our patients, and Dr. Boyd has observed continuous clinical activity without a remission for ninety-five days.

Of the 300 patients studied for immune response in this series, 208 white and 8 negro patients received primary vivax inoculations. Of the white patients, twenty-three exhibited the partially immune type of response and required additional inocula-

tions. Three of the negroes had hyperimmune reactions, two immune reactions and three partially immune reactions. None of the negroes experienced susceptible courses with vivax malaria.

The daily parasite count was particularly helpful in following the quartan infections which were used routinely as the primary inoculation species in the remainder of the negro patients. The incubation period of quartan malaria following intravenous inoculation averages between twelve and fifteen days. A rising parasite level in the blood gives assurance that a febrile course will ensue. Parasitemia failing to exceed 3,000 per c. mm. thirty days following inoculation, with absence of any fever above 103°F., is fairly good evidence that the patient has a relatively high degree of immunity and that some other form of therapy is indicated. The history was of no value in forecasting an immune reaction in the negro patients. In our series, seven of the negroes inoculated with quartan malaria did not complete susceptible courses and required additional fever therapy, two with falciparum malaria and four with hypertherm cabinet therapy.

These observations led to standardization of rules governing the inoculation of neurosyphilis patients with therapeutic malaria. White candidates from the United States who present a history of previous natural infection, individuals from the Mediterranean area or Puerto Rico and all negroes should be routinely inoculated with quartan malaria. Vivax malaria is the species of choice in all other white patients. Of those

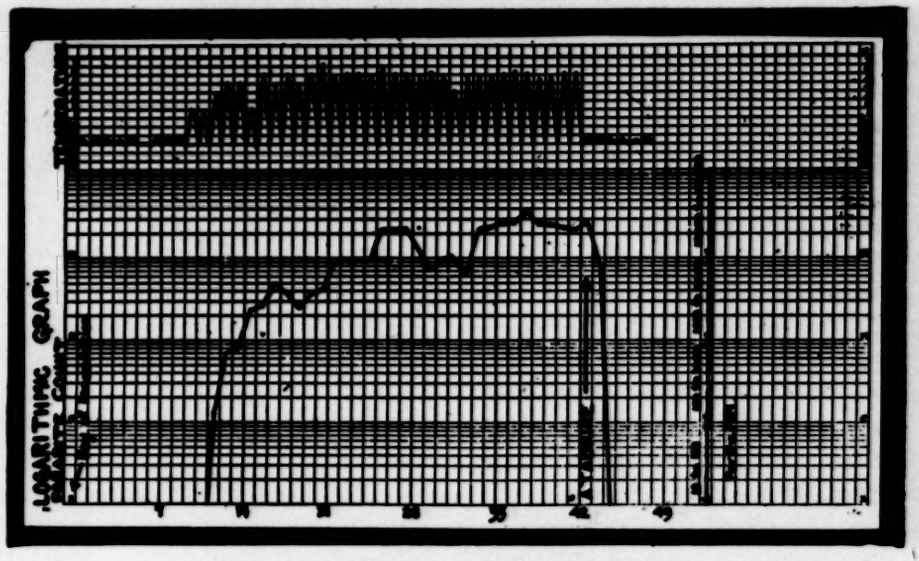


FIG. 3. The hypersusceptible response.

in this latter group who then experience a spontaneous remission prior to completion of therapy, those who have initially completed less than five paroxysms should be reinoculated with quartan malaria. Those who have experienced more than five paroxysms may be satisfactorily reinoculated with a heterologous strain of vivax malaria.

Quantitative Inoculations of Malaria Parasites. In addition to its use in permitting the early recognition of exuberant or runaway infections and early forecast of immune types of reaction which require termination of a morbidity-producing but therapeutically unsatisfactory parasitemia, the quantitative parasite count establishes more precise control over the methods of malaria inoculation and the subsequent febrile courses.[5]

It is becoming well recognized that the majority of vivax infections, either naturally or artificially induced, exhibit quotidian cycles with varying degrees of irregularity

rather than the commonly described pure tertian cycle. Following either mosquito inoculation or use of inocula of 5 to 10 cc. of infected blood without reference to parasite density, a number of days of remittent fever, characterized by continuous low grade temperature elevations of 101 to 103°F. and accompanied by severe malaise and exhaustion, is experienced. This irregular febrile course frequently debilitates patients prior to the establishment of true malaria paroxysms which are considered to be the essential feature of the therapeutic disease.

This initial period of remittent fever is probably the result of asynchronization of different broods of malaria parasites, apparently produced by the injection of large numbers of organisms in different stages of schizogony. Synchronization of broods occurring only after several days of clinical activity permits domination by a single brood and cycle. If a single parasite could be injected into the blood stream, only one brood of parasites would mature and only one cycle of paroxysms, typically tertian, presumably would ensue. Inoculation of single trophozoites has been accomplished successfully by the use of a micropipette at the Station for Malaria Research, Tallahassee, Florida, but the technic is time-consuming, requires the utmost skill and cannot yet practicably be applied clinically. However, in an effort to reduce remittent fever to a minimum, we have employed the quantitative parasite count in a technic of inoculation based on predetermined parasite doses low enough either to suppress or completely to eliminate this disturbing period of fever in most patients.

In this study duration of the period of remittent fever and the type of subsequent febrile cycle were analyzed in a series of 205 white patients who experienced susceptible reactions to inoculation with vivax malaria. The susceptible response was a necessary prerequisite since it was discovered earlier that the type of cycle and the intensity of remittent fever were dependent not alone on the technic of inoculation but also on the degree of malaria immunity of the individual patient. The technics of inoculation used in this investigation included: mosquito inoculation with a minimum of two infected mosquitoes applied per patient; intradermal inoculation with a total of 0.2 cc. of blood averaging a parasite count of 5,000 per c. mm. (total dose, 1 to 2 million parasites intracutaneously); and intravenous inoculation with total doses varying from 1 to 150 million parasites, determined by using graded inocula of 0.05 to 10.0 cc. of blood with different parasite densities. The quantitative parasite dose of donor's blood was determined in the following manner: quantitative parasite count of donor's blood = 5,000/c. mm.; inoculum of 1.0 cc. = 5 million parasites; inoculum of 0.2 cc. = 1 million parasites; inoculum of 10.0 cc. = 50 million parasites.

TABLE I
SUMMARY OF DATA

Method of Inoculation	No. Patients Inoculated	% with Tertian Cycles	Distribution of Patients (%) by Period (days) of Remittent Fever					
			0	1	2	3	4	5
Intradermal	26	57.8	42.3	23.1	11.5	19.3	0.0	3.8
Mosquito	58	22.4	8.6	17.2	12.1	32.8	15.5	13.8
Intravenous (1–5 m)	56	37.5	23.2	17.8	17.8	17.8	16.2	7.2
Intravenous (6–25 m)	29	31.0	13.8	10.3	31.0	24.1	13.8	7.0
Intravenous (26–150 m)	36	25.0	11.1	11.1	22.2	13.9	19.5	22.2
Intravenous (1 m)	28	42.9	35.7	17.9	14.3	14.3	14.3	3.5
Intravenous (2–5 m)	28	32.1	10.7	17.9	21.4	21.4	17.9	10.7

Table I summarizes the information obtained in this survey, indicating the number of patients inoculated by each technic, the type of subsequent febrile cycle and the percentages of patients by group, experiencing periods of remittent fever lasting zero, one, two, three, four or five days. The intravenous parasite doses were grouped for convenience into 1 to 5 million (further subdivided into 1 million and 2 to 5 million groups), 6 to 25 million and 26 to 150 million parasites.

Mosquito inoculation and intravenous inoculation with 26 to 150 million parasites produced the greatest number of long

periods of remittent fever. On the other hand, intradermal inoculation was followed by the least severe period of remittent fever, with 76.9 per cent of patients experiencing it for two days or less and 42.3 per cent not at all. However, the occurrence of 18.8 per cent (6 patients) unsuccessful "takes" as a result of technical difficulties excludes this method from routine clinical use.

Intravenous inoculations revealed that in susceptible patients the higher the parasite dose the longer the period of remittent fever in the greatest percentage of cases. The lower the parasite dose, the shorter and less severe is the remittent fever and the more closely does it resemble the results obtained following intradermal inoculation. Since total parasite doses of less than 1 million often require laborious dilution methods which appreciably diminish the clinical applicability of the technic, and since the 1 million parasite dose produces the most satisfactory reduction in remittent fever following intravenous inoculation (invariably resulting in successful "takes,") it is recommended as the standard inoculation procedure in vivax malaria therapy of neurosyphilis in susceptible white patients. The 1 million parasite dose eliminated the period of remittent fever in 35.7 per cent of patients and diminished it to two days or less in 67.9 per cent of patients in this study. In addition the greatest percentage of tertian cycles after intravenous inoculation followed the use of this parasite dose.

In brief summary then, the quantitative parasite count, a relatively simple laboratory procedure, can be of inestimable aid in determining the severity of a malaria infection and degree of the patient's resistance, in forecasting an immune response requiring intervention and retreatment, and in rather precisely regulating the febrile course by facilitating predetermined quantitative inoculations.

HETEROLOGOUS STRAINS OF PLASMODIUM VIVAX

Management of patients who experience partially immune types of reaction (group B, five to eight paroxysms) following inoculation with P. vivax has been simplified by the controlled use of heterologous strains of this species of malaria. Demonstration of the characteristics of homologous and heterologous strain immunity by the use of strains of P. vivax differing in geographic origin has provided an effective tool for completing therapeutic malaria courses in this partially immune group without requiring reinoculation with quartan malaria. The hazard of accidental transfusion malaria as a result of the prolonged latency of quartan infections, reportedly thirty years or more in some instances, and the prolonged hospitalization and morbidity occasioned by the lengthy incubation period and longer duration and cycle of paroxysms in these infections have raised justifiable objections to the use of this species in reinoculations.

Cross Inoculation Technic. The difference between substrains of the same species of malaria is best illustrated by the technic of cross inoculation,[6] whereby a heterologous strain produces definite clinical activity following the reinoculation of a patient who had previously experienced clinical activity with another strain. Five strains of P. vivax were utilized in our study of this strain difference. Strain M (Pv. McCoy) is the primary endemic strain of Southeastern United States, having been originally recovered in the Florida-Alabama area. Strains A, B, C and D were recovered from soldiers originally infected in the Southwest Pacific Islands of Guadalcanal, New Guinea and Bougainville.

Twenty-seven patients were completely studied by the technic of cross inoculation. In most instances the original vivax inoculation was performed intravenously, but a few successful mosquito and intradermal inoculations were also employed. Clinical activity following the original inoculation persisted until the occurrence of a spontaneous remission. No therapeutically interrupted original infections were included because of the greater possibility of active recurrence of the original strain later in the patient's

hospitalization. In spite of the negative histories of previous malaria attacks in twelve of the twenty-seven patients, most of them had some degree of malaria immunity at the onset with spontaneous remissions occurring prior to the exhaustion of the patient by a prolonged number of paroxysms. Reinoculation and further clinical activity was thus feasible within the therapeutic realm.

After the first spontaneous remission, quinine therapy (10 gr. per 50 pounds of body weight daily for five days) was withheld until the parasitemia decreased to submicroscopic densities. This was merely an added precaution in sterilizing the blood stream prior to reinoculation. Three to five days following completion of quinine therapy, an adequate interval for excretion of the drug, reinoculations with either homologous or heterologous vivax strains were accomplished intravenously. Following the reinoculation, clinical activity ensued until the development of a second spontaneous remission. Routine atabrine therapy was withheld until the second parasitemia was either negative or at insignificant levels at the end of two weeks following the last bout of clinical activity.

Reinfection Index. Since interest was primarily directed to the relationship of different vivax strains to each other and not to the varied individual immunity of patients prior to original inoculation, it became necessary to determine some factor which would largely cancel the effect of previous immunity on interpretation of the results of cross inoculation. The factor was designated the reinfection index, and was calculated in each case by considering the number of paroxysms experienced after reinfection as a percentage of the number of paroxysms experienced after original infection. For example, in the case of a patient developing eighteen paroxysms on original infection and two on reinfection, the index would be 11.1. On the other hand, in the case of a patient experiencing four paroxysms on original infection and two on reinfection, the index would be 50.0 in spite of an identical number of paroxysms following reinoculation. Previous individual immunity is thus largely eliminated from the analysis, and the higher the reinfection index the greater is the difference between the strains cross inoculated.

TABLE II
SUMMARY OF MEAN VALUES

Patients Reinfected with Homologous Strains (5):	
Duration of paroxysms following original infection	10.2
Duration of paroxysms following reinfection	1.0
Reinfection index	10.5
Patients Reinfected with Heterologous Strains (22):	
Duration of paroxysms following original infection	7.5
Duration of paroxysms following reinfection	4.5
Reinfection index	74.3
Individual Heterologous Reinfection Indices of Each Strain:	
M vs A, B, C, D	73.1
A vs M, B, C, D	78.8
B vs M, A, C, D	62.6
C vs M, A, B, D	70.0
D vs M, A, B, C	86.1

Heterologous Immunity. Table II lists the mean values of the results obtained in this cross inoculation study. It is apparent that heterologous immunity exists when reinfection of a patient with a strain of P. vivax differing in geographic origin from the original strain results in definite clinical activity sufficient for the completion of an interrupted course of therapeutic malaria. In this series of cases duration of the heterologous reinfection averaged 74.3 per cent (reinfection index) of the duration of the original infection, adequate activity for the completion of a course of treatment following a partially immune response with five or more paroxysms. Conversely, homologous immunity is characterized by the production of minimal clinical activity in patients reinfected with the same or similar substrain of vivax malaria. Duration of the homologous reinfection in this series averaged 10.5 per cent (reinfection index) of the duration of the original infection with that same strain, indicating clearly the futility of employing homologous strains as secondary agents for the completion of malaria therapy. From these observations, and from the recognized undesirability of reinoculat-

ing patients with quartan malaria when this is not necessary, heterologous strains of P. vivax are recommended for the reinoculation of white patients with neurosyphilis who experience group B partially immune types of original infection.

TEMPORARY DRUG INHIBITION OF THERAPEUTIC MALARIA

The frequent irregularity of therapeutic malaria infections has resulted in investigations designed to determine the value of various antimalarial agents in regulating or temporarily interrupting malaria paroxysms without permanent termination of the infections. Small doses of quinine, sulfonamides, arsenicals and intravenous 20 per cent dextrose solution have all been used from time to time, but were unsatisfactory chiefly because of their unpredictability in a given infection.

In 1939, Schwartz[7] first introduced sodium bismuth thioglycollate (thiobismol) as the most effective agent for reducing the frequency of paroxysms without completely eliminating them in vivax malaria. This work was confirmed by Brunsting and Love[8] and by Young, McLendon and Smarr,[9] who demonstrated quite clearly that thiobismol in 0.1 and 0.2 Gm. amounts had an inhibitory effect against half-grown vivax parasites. Paroxysms were frequently converted from quotidian to tertian periodicity, and usually remained tertian for the duration of the infection and often through several subsequent inoculations. The drug permitted a full course of therapy without causing exhaustion from daily febrile paroxysms, and also facilitated temporary interruptions when these were indicated by minor complications. Thiobismol had been employed similarly in quartan malaria but no consistent results, other than occasional unpredictable interruptions, could be obtained by these investigators.

A further study of the use of this drug in quartan malaria[10] was begun on our service when the accidental elimination of apparently half-grown P. malariae parasites followed administration of the drug to patients experiencing mixed vivax and quartan infections. A total of fifty-six injections of thiobismol, in doses of 0.1 and 0.2 Gm., were then administered intramuscularly at different intervals to thirty-eight patients experiencing true quartan (one paroxysm every three days), double quartan (two paroxysms every three days) and quotidian quartan (three paroxysms every three days) types of therapeutic malaria. Chance distribution of injections during the period of seventy-two hours from the onset of the main quartan paroxysm was permitted. Results of this investigation are presented in tabular form in Table III. For simplification of description the paroxysms occurring in true quartan cycle are referred to as the A paroxysms. Subsequent intermediate paroxysms occurring on the second or third day following the main cycle have been termed the B and C paroxysms respectively, and contribute in various combinations to the irregular double or quotidian quartan cycles. The parasite broods maturing during the respective paroxysms are similarly designated the A, B, and C broods. From the table it is noted that four types of cycles were encountered: A (true quartan), AB and CA (double quartan) and ABC (quotidian quartan). Those paroxysms remaining unaffected or which were specifically removed by injections of thiobismol are appropriately recorded in the table.

Eighty-seven and five-tenths per cent of the injections administered to patients with double quartan or quotidian quartan malaria resulted in temporary interruption and/or reduction in frequency of paroxysms. Partially grown parasites were uniformly affected in these cases, and no mature or very immature (less than one-third grown) parasites were influenced by the drug. Only 42.5 per cent of the injections given to patients having true quartan malaria was followed by temporary interruption. However, in all of these patients showing definite clinical effects only partially grown parasites (one-third, one-half or two-thirds grown) were inhibited. None of the five

TABLE III

CLINICAL EFFECTS OF THIOBISMOL ON QUARTAN MALARIA RELATED TO THE TIME OF ADMINISTRATION, AGE OF PARASITE BROODS AND PREVIOUS CYCLES

Time‡ of Administration	Age§ of Broods			True Quartan A				AB		Double Quartan		CA	Quotidian Quartan ABC				Total
	A	B	C	Removed	Interruption No Effect*	No Effect*	Total	A Removed	B Removed	Total	A Removed	Prolonged Interruption†	Total	A Removed	B Removed	B and C Removed	No Effect	Total	
±6	Mat.	2/3	1/3	..	5	6	11	..	4	4	..	..	..	..	..	1	..	1	16
7–8	1/6	5/6	1/2	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..	1
19–30	1/3	Mat.	2/3	2	6	8	16	1	..	1	..	3	3	..	..	..	2	2	22
31–42	1/2	1/6	5/6	2	..	2	4	..	..	..	..	..	..	1	..	..	..	1	5
43–54	2/3	1/3	Mat.	1	..	5	6	..	..	..	2	..	2	1	..	..	..	1	9
55–66	5/6	1/2	1/6	..	..	2	2	..	..	..	..	..	..	..	1	..	..	1	3
Total				5	12	23	40	1	4	5	2	3	5	2	1	1	2	6	56

* Interruption for four to eight days, with reappearance of the A cycle.
† Prolonged interruption for sixteen to thirty days after injection.
‡ Calculated as the number of hours from the onset of the main A paroxysm.
§ Listed as fractions of maturity, i.e., one-half equals half-grown parasites.

patients with original parasite densities above 10,000 parasites per cm. responded to thiobismol injections with definite clinical effects. Thus thiobismol appears to be an effective agent for reducing the frequency of paroxysms and regulating the febrile cycle in patients experiencing double quartan or quotidian quartan malaria with the usual parasite densities below 10,000 parasites per c. mm. This drug can, therefore, be equally useful in both vivax and quartan malaria infections, enabling neurosyphilis patients better to tolerate complete courses of therapy.

SUMMARY

1. Technical refinements of the treatment of neurosyphilis with induced malaria have long been overlooked. An appreciation of these aspects of treatment will lead to a sound clinical approach to the problem, to an understanding of the immune mechanisms involved, and to the wider adoption of technics which are relatively simple and which aid in the production of satisfactory courses of the disease.

2. The quantitative parasite count eliminates confusion and waste of time in the use of therapeutic malaria by materially aiding in determining the severity of a given malaria infection and the degree of the patient's resistance, in rapidly forecasting an immune response requiring intervention and retreatment without wasteful weeks or months of observation, and in the rather precise regulation of the febrile course by facilitating quantitative inoculations.

3. Heterologous strains of P. vivax have been shown to produce sufficient clinical activity in previously vivax-infected individuals to allow their routine use for the reinoculation of white neurosyphilis patients experiencing partially immune types of original infection (five to eight paroxysms) thus eliminating the undesirable use of quartan strains for reinfection.

4. Criteria for malaria inoculations in the treatment of neurosyphilis have been established: (1) White patients with a history of malaria, individuals from the Mediter-

ranean area, Puerto Rico, or highly endemic malaria zones, and all negroes should be primarily inoculated with quartan malaria, intravenously in large doses (more than 10 million parasites). (2) All other white patients without a history of malaria should be primarily inoculated with vivax malaria, intravenously in doses of 1 million parasites. (3) Patients in grcup B who develop partially immune responses with less than five paroxysms should be reinoculated with quartan malaria. (4) Patients in group B who develop partially immune responses with five paroxysms or more should be reinoculated with heterologous strains of vivax malaria.

5. Sodium bismuth thioglycollate (thiobismol), which inhibits partially grown parasites, can be employed to regulate both vivax and quartan infections when irregular cycles occur.

REFERENCES

1. Stokes, J. H., Strenberg, T. H., Schwartz, W. H., Mahoney, J. F. and Wood, W. B., Jr. The action of penicillin in late syphilis. *J. A. M. A.*, 126: 73–79, 1944.
2. Gammon, G. D., Stokes, J. H., Beerman, H., Ingraham, N. R., Lentz, J. W., Morgan, H. G., Steele, W. and Rose, E. K. Penicillin in neurosyphilis: effect on blood and spinal fluid. *J. A. M. A.*, 128: 653–654, 1945.
3. Earle, W. C. and Perez, M. Enumeration of parasites in the blood of malarial patients. *J. Lab. & Clin. Med.*, 17: 1124, 1932.
4. Becken, F. T., Kaplan, L. I., Read, H. S. and Boyd, M. F. Variations in susceptibility to therapeutic malaria. *Am. J. M. Sc.*, 211: 680–685, 1946.
5. Kaplan, L. I., Read, H. S., Becker, F. T. and Boyd, M. F. The use of quantitative parasite inoculation doses in therapeutic plasmodium vivax malaria. *Arch. Neurol. & Psychiat.*, 56: 65–73, 1946.
6. Kaplan, L. I., Read, H. S., Becker, F. T. and Boyd, M. F. Homologous and heterologous strains of plasmodium vivax: a cross-inoculation study of malaria strain immunity. *J. Lab. & Clin. Med.*, 31: 400–408, 1946.
7. Schwartz, W. F. The effect of thiobismol on therapeutic malaria. *J. Pharmacol. & Exper. Therap.*, 65: 175–184, 1939.
8. Brunsting, L. A. and Love, W. R. The tempering effect of sodium bismuth thioglycollate (thiobismol) on therapeutic malaria. *Proc. Staff Meet., Mayo Clin.*, 15: 285–288, 1940.
9. Young, M. D., McLendon, S. B. and Smarr, R. G. The selective action of thiobismol on induced malaria. *J. A. M. A.*, 122: 492–494, 1943.
10. Kaplan, L. I., Read, H. S. and Becker, F. T. The action of sodium bismuth thioglycollate on therapeutic quartan malaria. *J. Lab. & Clin. Med.*, 31: 735–741, 1946.

441 *E.* 20 *St.* 5407 *Atlantic Ave.*

Left Vocal Cord Paralysis Associated with Cardiac Disease*

DAVID A. DOLOWITZ, M.D. *and* C. S. LEWIS, M.D.
Salt Lake City, Utah

PARALYSIS of the left recurrent laryngeal nerve has been observed occasionally in association with cardiac enlargement, but a causal relationship is still questioned by many.[1] Those who believe that such a relationship exists are, in the main, unable to agree on the exact mechanism involved. This paper adds two cases of the syndrome to those which have been reported. Anatomic studies of the recurrent laryngeal nerve were also made in twenty-five cadavers. From these studies a plausible hypothesis is presented for consideration. It is based on anatomic evidence which may elucidate this unusual syndrome.

The first examples of vocal cord paralysis in heart disease were described by Ortner[2] in 1897 when he reported two cases of mitral stenosis with left vocal cord palsy. The autopsies confirmed the diagnosis of mitral stenosis. In the first case the left recurrent nerve was caught between the left atrium and the left bronchus and in the second instance between the left atrium and the aortic arch.

In 1911 Fetterolf and Norris[3] collected thirty-seven cases from the literature and added one of their own. In reviewing these cases, and in reporting their own anatomic study, they concluded that (1) the nerve must be "squeezed" between the left pulmonary artery and the aortic arch or the ligamentum arteriosum and (2) any factor causing dilatation or upward displacement of the left atrium, the left pulmonary vein or the left pulmonary artery would tend to cause impingement on the nerve. In disagreement with Ortner these authors emphasized that it would be impossible for the atrium to press directly on the aorta or bronchus, pinching the nerve. They pointed out that some of the cases reported as mitral stenosis were complicated by inflammatory conditions. Pericardial effusion, pericarditis, aneurysm of the aorta or the pulmonary artery, or enlarged peribronchial lymph nodes may have caused pressure on the nerve resulting in paralysis. Fetterolf and Norris cast doubt on an explanation previously advanced by Kraus[4] in which he claimed that the nerve was paralyzed by being pulled down by the aortic arch. The traction is due to an enlarged right ventricle.

In 1934 King, Hitzig and Fishberg[5] presented three cases of arteriosclerotic heart disease with left ventricular failure (two of which were complicated by myocardial infarction) in which left vocal cord paralysis was present. They assumed that the palsy was caused by compression of the nerve between the left pulmonary artery, the aorta and the ligamentum arteriosum. Their explanation differs from that of others by the stress placed upon dynamic dilatation of the pulmonary vessels as an important factor in causing compression of the nerve. They pointed out that this may be revealed by radioscopic examination but might not be detected at autopsy.

Erlanger and Levine[6] presented two cases of congenital atrial septal defect with recurrent laryngeal nerve palsy and cited five other cases of congenital heart disease accompanied by hoarseness, one of which was an example of the so-called Lutembacher's syndrome (mitral stenosis plus atrial septal defect). In all the cases con-

* From the Departments of Medicine and Surgery, University of Utah School of Medicine, Salt Lake City, Utah.

spicuous enlargement of the pulmonary artery was present. The nerve palsy in these cases, the authors concluded, was best explained by the mechanism proposed by Fetterolf and Norris.[3]

Notkin[7] agreed with the explanation of Fetterolf and Norris and of King, Hitzig and Fishberg[5] but suggested in addition that thrombi in the auricle, thrombosis of the pulmonary artery, atheromas and sclerosis of the pulmonary artery may become contributory factors. It was presumed by these authors that the focal induration produced by these lesions exerts more effective pressure than soft tissue. This explanation was supported by Price[8] and Wallerstein.[9]

Arguments against a causal relationship between cardiac disease and left recurrent laryngeal nerve palsy are chiefly based on the fact that while mitral stenosis is a rather common condition, associated left vocal cord paralysis is quite rare. Smith, Lambert and Wallace[10] reported 235 cases of paralysis of the recurrent laryngeal nerve. Only five of these cases were associated with heart disease; an additional thirty-four were accompanied by aneurysm of the aorta. Reiche[11] reviewed 300 cases of mitral stenosis and found left recurrent laryngeal palsy in only two instances. Scheifley and Smith[1] reviewed 223 cases of left laryngeal palsy and found mitral stenosis as the presumable causative agent in ten cases. They pointed out, however, that in 51 per cent of their cases no cause for the paralysis was found. Scheifley and Smith assumed that heart disease may have been present in some cases in this group. They found that while the incidence of mitral stenosis in a general clinic population (Mayo) was 0.5 per cent, this type of heart disease was present in 5.0 per cent of 223 patients with left recurrent laryngeal nerve palsy. Therefore, it was noted that mitral stenosis was ten times as frequent in cases of left recurrent laryngeal nerve palsy as in a control group. In another group of patients with right cord paralysis no cases of mitral stenosis were found.

Apparently the causal relationship between cardiac enlargement and recurrent nerve palsy is not established conclusively. If a causal relationship does exist, the mechanism is not fully understood. The two following instances of the syndrome are being reported to add to the available data on this condition:

CASE REPORTS

CASE 1. C. R. (8855), a twenty-five year old single, white male entered the Salt Lake General Hospital on February 19, 1946, because of severe congestive heart failure. About one month prior to admission the patient had contracted a febrile illness characterized by cough, fever, general malaise, dyspnea, orthopnea, a sense of epigastric pressure and fatigue. The cough, fever and malaise disappeared after two weeks but symptoms of cardiac embarrassment progressed. About four days prior to admission the patient noted edema of the feet and legs. At that time he was unable to sleep for more than thirty minutes at a time. The history revealed symptoms suggestive of acute attacks of rheumatic fever at the ages of eight and twelve years. He then enjoyed a normal life with usual activity until four years prior to admission when he began to restrict his activities because of dyspnea on exertion and a feeling of abdominal fullness. The family history was not contributory.

On physical examination the patient appeared markedly dyspneic and orthopneic, and displayed slight cyanosis of the lips and nail beds. Minimal clubbing of the fingers was noted. The neck veins showed systolic pulsation. Percussion of the chest revealed dullness over the right base posteriorly with markedly diminished breath and voice sounds over this area. Moist râles were heard at both lung bases posteriorly. On percussion the heart was enlarged to the left anterior axillary line and the point of maximum impulse was located in the sixth intercostal space in the left anterior axillary line. The rhythm was regular. A systolic murmur was heard over the apex and this was transmitted to the axilla. A low pitched diastolic rumble, which was localized in the apical region, and a high pitched early diastolic murmur were audible over the aortic area. The abdomen was somewhat distended and a fluid wave and shifting dullness were demonstrable. The edge of the liver which was firm and smooth was palpated 7 cm. below the right costal margin. There was

pitting edema of the lower extremities extending to the thighs. The temperature was 98.4°F., the pulse 78 and the respirations 22. The blood pressure was 130 systolic and 85 diastolic.

All the laboratory findings were within the normal range except for measurements of venous pressure (265 mm. of saline) and circulation time (decholin, 37 seconds). Vital capacity was 67 per cent of normal. Blood urea nitrogen was 32 mg. per cent on admission and 22 mg. per cent one week later. Urine was normal.

A roentgenogram of the chest revealed congestion of the lung fields with elevation of the right leaf of the diaphragm. The heart was enlarged in all diameters with the apex at the seventh rib anteriorly. There was marked prominence of the right cardiac border, the left atrial segment and the left pulmonary artery.

The electrocardiogram showed right axis deviation with very large P waves in leads I and II and U-shaped depression of the ST segment with inversion of T in leads II and III. The tracing was thought to be indicative of right ventricular and left atrial enlargement. The changes in the ST segment were assumed to be due to digitalis therapy. A clinical diagnosis of rheumatic heart disease with involvement of the mitral and aortic valves was made.

The patient improved following treatment with bed rest, diuretics, low sodium diet and digitalis. On the second hospital day the patient was noted to be slightly hoarse. Examination of the throat was negative but the hoarseness persisted. On the sixth hospital day, at a time when by clinical and roentgenographic examination the heart was decreasing in size, laryngoscopic examination revealed sluggish movement of the left vocal cord. On the eighth hospital day the left cord was completely paralyzed. As the patient improved the heart continued to decrease in size. The voice improved to a certain extent. The left cord, however, remained in cadaveric position and the right cord gradually crossed the midline to meet it. This condition has remained constant during the six months that the patient has been observed although the fixed left cord is gradually shifting toward a midline position with accompanying vocal improvement.

CASE II. R. B. (8696), a thirty-four year old housewife, entered the Salt Lake General Hospital on March 19, 1946, because of shortness of breath, difficulty in breathing while lying down and swelling of the ankles. These difficulties had been present for four months and had become progressively more severe. Orthopnea and dependent edema soon developed. The patient was told that she had heart trouble at the age of seven years. She was kept out of school for one year because of "leakage of the heart." However, she married and went through three successive pregnancies without apparent difficulties. Two and one-half years before admission, following birth of her third child, the patient had an attack of the "flu" and was kept in bed. Hoarseness was first noted at that time and has persisted ever since. Her private physician examined the larynx and reported paralysis of the left vocal cord. About a year before admission the hoarseness improved to a point at which she could teach Sunday school. Since the onset of the present illness, the hoarseness recurred. The family history was not contributory.

Physical examination revealed a well proportioned white woman who spoke in a hoarse whisper. She was dyspneic, slightly cyanotic and presented a distinct malar flush. The chest was clear except for a few moist râles in both lungs posteriorly. Mild emphysema was present. The heart was enlarged to the left anterior axillary line and the point of maximum impulse was located in the fifth intercostal space. A harsh, high pitched systolic murmur was heard at the apex and along the left sternal border. The second aortic sound was louder than the second pulmonic sound. The rhythm was regular. The abdomen was somewhat distended and a fluid wave was present. The liver was enlarged to 8 cm. below the right costal margin, its edge being firm and smooth. Marked pitting edema of the ankles was present. Laryngoscopic examination revealed paralysis of the left vocal cord which remained in the cadaveric position of phonation. The right vocal cord did not cross the midline. The temperature was 98.6°F., the pulse 80 and the respirations 24. The blood pressure was 130 systolic and 70 diastolic.

The red blood cell count was 4.3 million per cu. mm., the hemoglobin was 12.3 Gm. and the volume of packed red cells was 39 cc. per 100 cc. of blood. The erythrocyte sedimentation rate was normal. The white blood cell count was 6,900 per cu. mm. and the differential count was normal. The Kahn test of the blood was negative; the venous pressure was 190 mm. of saline and the circulation time (decholin) was 25 seconds. The urine was normal. The blood urea

nitrogen was 15.5 mg. per cent and the total blood protein was 6.1 Gm. per cent, with 4.2 Gm. albumin and 1.9 Gm. globulin.

Roentgenographic examination of the chest revealed generalized enlargement of the cardiac silhouette. The apex of the heart lay in the eighth interspace. The right border of the heart extended far to the right of the midline. These findings were interpreted as indicating the presence of marked right atrial enlargement, right ventricular enlargement and some left ventricular enlargement. The aortic shadow was not visualized. The shadow of the pulmonary artery was very prominent. The pulmonary arteries were extremely dilated, and their finer ramifications extended out to the periphery of the lung field. The superior vena cava was visualized. In the right anterior oblique view the cardiac silhouette was seen to occupy practically the entire mediastinum, displacing the esophagus posteriorly. The barium-filled esophagus showed a marked indentation in the region of the pulmonary artery but no compression, suggesting left atrial enlargement. No aortic shadow could be seen. Fluoroscopy confirmed these findings and in addition revealed a marked "hilar dance."

The electrocardiogram showed a normal sinus rhythm with normally shaped P waves. The QRS complexes appeared notched and slurred and measured 0.14 seconds in width. A deep S wave was present in lead I and serial precordial leads revealed late activation of the right ventricular epicardial surface. Right axis deviation was present. RT junction appeared depressed in leads II and III. The curve was interpreted as an example of right bundle branch block with right ventricular enlargement. No atrial enlargement could be demonstrated. The clinical impression was that of an atrial septal defect. The presence of an associated mitral stenosis was suspected but could not be substantiated.

As the patient improved following appropriate management, it was noted that the voice became stronger. The right cord was seen to cross the midline and approximate the left, which remained in the cadaveric position.

COMMENTS

These two cases present the triad of (1) an enlarged heart, (2) increased pressure in the pulmonary circuit with resultant enlargement of the pulmonary conus and the right ventricle and (3) left recurrent nerve palsy. The first patient was thought to have rheumatic involvement of the mitral and aortic valve with marked enlargement of the left atrium. The second patient was thought to have an atrial septal defect, possibly with mitral stenosis (Lutembacher's syndrome) and an enormous increase in the size of the pulmonary conus.

In reviewing the literature one is impressed by the fact that while left recurrent laryngeal palsy associated with heart disease is uncommon, the combination occurs too often to be merely coincidental. There has been much disagreement as to the mechanism by which an enlarged heart produces pressure on the recurrent laryngeal nerve. Too often a single factor has been proposed in explanation of all the cases. We believe that this view is not justified.

There seems to be no reason why a variety of anatomic lesions (mitral stenosis, arteriosclerotic heart disease with and without coronary occlusion, congenital heart disease and aneurysms of the large vessels) may not produce the syndrome. The left recurrent laryngeal nerve passes under the aorta in such a manner that it is in close approximation with the aorta, the ligamentum arteriosum and the pulmonary artery. These three structures form a triangle through which the nerve usually passes. In addition to dilatation or changes in position in any one of these structures their relationship may become altered by pressure exerted upon them, for example, by an enlarged left atrium. We are not in a position to say whether or not the left atrium can exert pressure directly on the nerve. We do believe, however, that changes in size or relationship of any one of a number of mediastinal structures is potentially capable of causing pressure on the recurrent laryngeal nerve. We believe that the explanation of Fetterolf and Norris[3] is the most logical. These authors have assumed that the dilated heart transmits pressure through the pulmonary vessels, pressing the nerve against the aorta. Furthermore, back pressure in the pulmonary circuit with

resulting enlargement of the pulmonary vessels (King, Hitzig and Fishberg)[5] seems to be compatible with this assumption.

It is interesting to speculate as to whether pressure alone, traction alone or both combined cause devitalization of the nerve and over how long a period this pressure must be applied. Judd, New and Mann,[12] working with dogs, found that pinching the nerve once "with a hemostat in a manner similar to that necessary to stop hemorrhage from a small vessel" will cause a temporary paralysis for thirty to ninety days depending on the anatomic point at which the nerve was pinched. The function of the nerve always returned. They also found that ligating the nerve with any type of suture material resulted in permanent paralysis. This would infer an inflammatory "ligature" about the nerve. When tissues as soft as the heart and great vessels are involved, it is hard to imagine a crushing injury so severe that the nerve could not recover. This view is strengthened by the findings in the first case in which the initial symptoms of paralysis appeared when the heart clinically and roentgenographically was decreasing in size. The voice change incurred while the heart was enlarged has not changed in over six months. The second case is of less help; although paralysis accompanied a bout of decompensation, exact x-ray studies were not made.

Despite the little attention paid Kraus's theory[4] of tension traction causing the injury, it is hard to explain this away since aortic aneurysm remains the most frequent cause of paralysis in cardiac conditions. Further study is indicated.

Left laryngeal nerve palsy with cardiac enlargement is uncommon, and it must be assumed that in addition to the contributing factors listed certain inherent anatomic relationships between the structures of the mediastinum must be present before the nerve can be compressed. A potential space the size of a small lima bean exists in the critical triangle. It is possible that the degree of pressure, the length of time over which it is applied, and inflammatory changes in the nerve may be contributory factors resulting in nerve paralysis. This view is strengthened by the first case in which paralysis occurred while the heart was shrinking in size and cardiac function was improving. Antecedent damage at the time when cardiac damage was maximal is thus suggested. Decreased compression of the nerve with reduction in the size of the heart while relieving the "compression" would not invalidate this hypothesis.

Careful anatomic study* of the area probably concerned in the production of this syndrome was made in five fresh and twenty-two fixed cadavers. In the area bounded by the aortic arch superiorly, the pulmonary artery inferiorly and the ligamentum arteriosum medially, one constantly finds a group of three to five lateral tracheobronchial lymph nodes. These nodes are always in close proximity to the left recurrent laryngeal nerve as it leaves the vagus nerve and loops around the aortic arch. They vary in size from 3 mm. in each dimension to 2 cm. by 1 cm. by ½ cm.

In three of the cadavers studied one of these lateral tracheobronchial lymph nodes was firmly adherent to the vagus nerve. In one body, in addition to the larger node in contact with the vagus nerve, a smaller node was firmly anchored to the left recurrent laryngeal nerve immediately beyond its origin from the vagus nerve. (Fig. 1.) In this instance the left atrium and the pulmonary artery lymph node could conceivably compress the left recurrent laryngeal nerve against the aorta sufficiently to result in nerve fiber degeneration.

We believe that hypertrophy of a strategically placed lymph node can cause fixation of the left recurrent laryngeal nerve. This fixation could permit pressure on the nerve by either cardiac enlargement or pulmonary artery engorgement or both. These anatomic observations are considered so pertinent that additional studies are now under way.

* The anatomic studies were made by one of us (D. A. D.) under the direction of Dr. C. A. Swinyard, Professor of Anatomy, University of Utah.

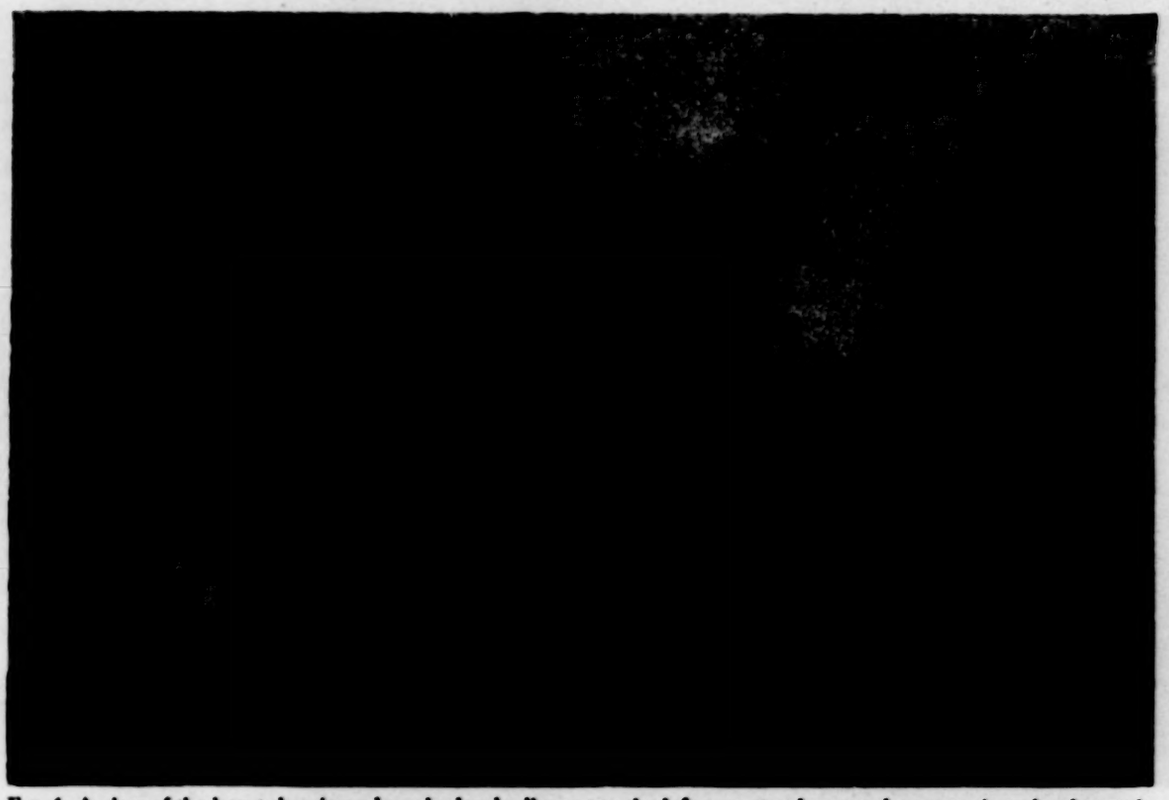


FIG. 1. A view of the heart showing a lymph gland adherent to the left recurrent laryngeal nerve as it arches beneath the aorta. A, left recurrent laryngeal nerve; B, arch of aorta; C, lymph nodes; D, ductus arteriosus; E, left pulmonary artery; F, vagus.

Prognosis is good as to return of the voice. Some instances of vocal paralysis, with subsequent return of function of the affected cord, have been reported. Even in patients in whom there is permanent paralysis of a vocal cord the voice may recover to a variable extent. This improvement is due to compensation by the right cord which gradually crosses the midline to meet the left cord. Some of the cases that have complete voice return may have been due to intrinsic disease within the larynx and not to nerve palsy. This can best be illustrated by two cases of mitral stenosis seen by one of us (D. A. D.). In these cases the hoarseness was due to chronic laryngitis so severe as to impede the motion of both cords. Biopsy of the false cord confirmed the impression of intrinsic disease and with voice rest the condition gradually improved.

SUMMARY

1. Two examples of paralysis of the left recurrent nerve associated with heart failure are reported. One patient developed this paralysis as a sequel to rheumatic heart disease with severe valvular lesions. The second patient developed hoarseness secondary to congenital deformity of the heart.

2. Many mechanisms have been proposed to explain the syndrome of left recurrent nerve palsy associated with cardiac disease. A review of these hypotheses shows that none fully explains the condition.

3. It appears from our anatomic studies that the lymph nodes in the triangle formed by the pulmonary artery, aortic arch and ligamentum arteriosum may effectively compress the left recurrent laryngeal nerve when accompanied by cardiac hypertrophy, pulmonary artery engorgement, or both.

REFERENCES

1. SCHEIFLEY, C. H. and SMITH, H. L. Mitral stenosis and paralysis of the left recurrent laryngeal nerve. *Minnesota M. J.*, 25: 362, 1942.
2. ORTNER, NORBERT. Recurrenslähmung bei Mitralstenose. *Wien. klin. Wchnschr.*, 10: 753, 1897.
3. FETTEROLF, G. and NORRIS, G. W. The anatomical

explanation of the paralysis of the left recurrent laryngeal nerve found in certain cases of mitral stenosis. *Am. J. M. Sc.*, 141: 625, 1911.

4. KRAUS.[3]
5. KING, F. H., HITZIG, W. M. and FISHBERG, A. M. Recurrent laryngeal paralysis in left ventricular failure. *Am. J. M. Sc.*, 188: 691, 1934.
6. ERLANGER, H. and LEVINE, S. A. Atrial septal defect. A report of two cases in which there was recurrent laryngeal nerve paralysis, *Am. Heart J.*, 26: 520, 1943.
7. NOTKIN, M. Paralysis of the left recurrent laryngeal nerve in mitral stenosis. *Arch. Int. Med.*, 33: 71, 1924.
8. PRICE, G. E. Paralysis of the left recurrent laryngeal nerve in association with mitral stenosis. *J. A. M. A.*, 82: 1251, 1924.
9. WALLERSTEIN, E. U. Paralysis of the left recurrent laryngeal nerve in association with mitral stenosis. *Virginia M. Monthly*, 53: 298, 1926.
10. SMITH, A. B., LAMBERT, V. F. and WALLACE, H. L. Paralysis of the recurrent laryngeal nerve. *Edinburgh M. J.*, 40: 344, 1933.
11. REICHE, F. Paralysis of the left recurrent laryngeal nerve in mitral stenosis. *Med. Klin.*, 22: 1142, 1926.
12. MANN, F. C., JUDD, E. S. and NEW, G. B. The effect of trauma upon the laryngeal nerves. *Ann. Surg.*, 67: 257, 1918.

Parenteral Benadryl in Allergy*

SIDNEY FRIEDLAENDER, M. D. *and* ALEX S. FRIEDLAENDER, M. D.
Detroit, Michigan

WIDE clinical experience has demonstrated that oral administration of antihistamine drugs is frequently successful in temporarily alleviating symptoms in various allergic syndromes. The response to this form of medication varies greatly from one individual to another, depending to some extent on the site of allergic involvement as well as upon the intensity of symptoms. Certain types of allergic reactions, namely, those involving the skin, are more frequently controlled by these agents than are those in which the nasal and bronchial mucosa are the site of difficulty. It is of course possible that histamine plays a greater rôle in some allergic conditions than in others, or that the amount of histamine release in certain instances is too great to be controlled adequately by the usual non-toxic oral doses of the antihistamine drugs. There is also the consideration that the variable effect observed in similar cases may be related to differences in gastrointestinal absorption of the drugs. Occasionally, an increase in the amount of drug administered orally may be successful in controlling symptoms. When larger doses are used, however, side effects become more frequent and pronounced. For the usual ambulatory patient this side action limits the amount of drug that may be safely given. In the acutely ill patient the very common side effect of drowsiness is not a contraindication to the use of larger doses, and in severe allergic states sedation is often desirable. Very frequently, however, even large oral doses fail to produce symptomatic relief. In these cases parenteral administration of antihistamine drugs deserves consideration.

For some time we have had available for clinical trial a solution of benadryl hydrochloride* containing 10 mg. per cc., suitable for parenteral administration. The action of this preparation was studied in twenty-five patients with severe allergic symptoms who either were not benefitted by large oral doses of benadryl and other antihistamine drugs or to whom for some reason it was not practical to administer such medication orally. In most cases the drug was given intravenously but in some instances it was administered intramuscularly or subcutaneously. Urticaria and angioneurotic edema of a severe degree was present in fifteen patients. One of these was an infant of twelve months; the remainder were adults. Nine other patients were in "status asthmaticus" while one patient had severe migraine, allergic in nature.

Early in the use of this preparation it was learned that relatively small doses administered intravenously often produced a profound hypnotic effect. For this reason the initial injection in each case was carried out in the home or hospital. Ten mg. (1 cc.) of the drug was given slowly as the first intravenous dose and the effect observed. If relief of symptoms did not occur promptly and sedation was not marked, a second dose of 20 to 30 mg. (2 to 3 cc.) was repeated two hours later. In most cases 30 mg. intravenously exerted a marked sedative action lasting several hours and often induced sleep. In some instances 50 mg. (5 cc.) doses were necessary to produce this effect. While sedation appeared to be the most consistent effect of intravenous benadryl, very marked symptomatic relief occurred in certain patients who had not been favorably

* Benadryl hydrochloride supplied by Research Dept., Parke, Davis & Co., Detroit, Mich.

* From the Departments of Bacteriology and Medicine, Wayne University College of Medicine, Detroit, Mich.

affected by considerably higher doses of the oral preparation.

The value of parenteral benadryl in urticaria was impressed upon us very early in this study by its dramatic effect in a man of forty-nine, seriously ill with generalized urticaria and angioneurotic edema of five weeks' duration. Large oral doses of benadryl as well as two other antihistamine drugs had failed to alleviate symptoms. The sudden onset of severe gastrointestinal hemorrhage further complicated the problem in this instance. Since morphine in repeated doses failed to control the restlessness and hematemesis, an initial dose of 10 mg. of benadryl was given intravenously. Only slight drowsiness occurred and a second dose of 30 mg. was given two hours later. Within a few moments the skin swellings noticeably diminished and the patient slept for the first time in several days. The same amount was repeated in three hours when the patient awakened complaining of pruritus. It was found necessary to administer 30 mg. at four-hour intervals during the next two days in order to control symptoms. Following the initial dose of benadryl, hematemesis ceased although stools remained tarry in nature for several days and occult blood was present for a week thereafter. With improvement of the patient's condition the effect of intramuscular and subcutaneous administration of benadryl was observed. Control of symptoms with less drowsiness occurred when given in this manner although slight local discomfort followed each injection. The patient preferred the subcutaneous to the intramuscular site and was able to administer the drug himself subcutaneously following discharge from the hospital. During the next two months, while under allergic study, he gave himself 10 to 20 mg. of the injectable benadryl once or twice daily to control urticarial symptoms. Repeated trial of oral antihistaminics continued to be without effect. No evidence of acute or chronic toxicity was noted during or after the prolonged use of the drug by injection.

Parenteral benadryl was found very helpful in twelve cases of severe "serum-sickness type" reaction following the use of penicillin. In contrast to many similar cases which are helped by oral administration of antihistamine drugs, the patients in this group failed to benefit from such medication during the acute stages of their difficulty. Benadryl given intravenously in doses of 10 to 30 mg. was usually effective in alleviating edema, pruritus and arthralgias for periods of four to twelve hours. Later in the course of these "serum-sickness type" reactions, when dermographism appeared to be the principal remaining symptom, oral antihistaminics seemed to exert sufficient palliative action to warrant discontinuance of the intravenous material. A year old infant suffering from a severe penicillin reaction was benefitted remarkably by intramuscular injections of 5 to 10 mg. of benadryl every four to six hours over a period of a week. Despite the very marked palliative action it cannot be said at this time that the course of the penicillin reactions in these cases was perceptibly shortened by the intravenous use of the drug. In a severe case of acute urticaria due to aspirin, and in another case following a prophylactic dose of tetanus antitoxin in which no help was afforded by oral medication, control of symptoms was possible by the intravenous injection of benadryl.

Our experience with intravenous benadryl in nine cases of "status asthmaticus" indicates that its principal value in such patients lies in its sedative and hypnotic action. While reduction in the amount of asthma has been observed in some instances following the administration of 30 to 50 mg. intravenously, the effect has not been consistent enough on repeated administration to warrant its use to the exclusion of such valuable drugs as ephedrine, adrenalin, aminophyllin and iodides. In most cases, it has been of definite help through the production of a sedative effect so frequently desired in patients with severe asthma.

Intravenous benadryl was also used in a young woman with severe migraine of long standing in whom milk sensitivity was an important etiologic factor. During a par-

ticularly severe episode when usual measures, aside from opiates, were unsuccessful in relieving pain or inducing sleep, a 50 mg. dose of benadryl intravenously produced satisfactory sedation. This dose has been repeated on subsequent occasions during acute upsets with the same helpful effect.

Although comparatively little is yet known of the absorption, utilization and excretion of the antihistaminics, the potency of small intravenous doses suggests that only partial utilization of the drug may occur when given orally. It appears at this time that injectable benadryl should be used cautiously, and should be confined to those patients in whom it is reasonable to expect that antihistamine therapy would be of value and in whom the oral medication cannot be given or has proved ineffective. With these factors in mind, it often serves as a helpful adjunct in the management of difficult cases. Present evidence indicates that antihistamine therapy, whether given orally or by injection, is a palliative and not a curative measure. The underlying allergic factors in each case must be carefully searched for and evaluated in order to determine the specific therapy necessary.

SUMMARY

A preparation of benadryl hydrochloride containing 10 mg. per cc., suitable for parenteral injection, was found beneficial in controlling symptoms in many severe cases of generalized urticaria and angioneurotic edema. The marked sedative and hypnotic action obtained from small intravenous doses was also considered a helpful adjunct in the treatment of "status asthmaticus."

Review

Rickettsialpox in New York City*

MORRIS GREENBERG, M.D.
New York, New York

RICKETTSIALPOX is a disease of rickettsial origin first recognized in New York City in 1946 in the course of the investigation of an epidemic of an exanthematous disease. It is characterized clinically by the appearance of an initial lesion somewhere on the body, followed in about one-half to one week by an acute onset of illness with fever, headache, backache and other symptoms and finally by a generalized papulovesicular rash. The acute illness and rash last about one week each, and the entire course from onset of the initial lesion is about three weeks.

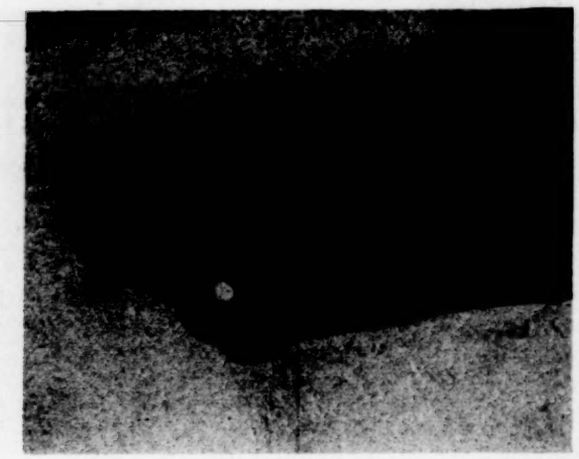


FIG. 1. Initial lesion of rickettsialpox in interdigital space between fourth and fifth toes. (A button has been placed between the toes to bring out the lesion more clearly.) (GREENBERG and PELLITTERI. *Bull. New York Acad. Med.*, June, 1947.)

CLINICAL FINDINGS

The disease is characterized clinically[1] by a triad consisting of: (1) an initial lesion followed in about three days to a week by (2) an abrupt onset of fever and other symptoms and a little later by (3) a papulovesicular rash.

1. *Initial Lesion.* The initial lesion begins as a rounded firm, red papule which grows in size until it attains a diameter varying from 1 to 1½ cm. The center of the papule becomes vesiculated within a few days after onset, the vesicle then shrinks and dries forming a black eschar. (Figs. 1 and 2.) The skin around the papule is at first normal but later becomes erythematous. The lesion is not tender nor does it itch. Patients are frequently unaware of the initial lesion until it is called to their attention later in the disease. After about three weeks the scab falls off leaving a small scar. The regional nodes usually become enlarged but are not tender or only slightly tender to the touch.

FIG. 2. Primary lesion on the left arm in crusted stage. (GREENBERG, PELLITTERI, KLEIN and HUEBNER. *J. A. M. A.*, March 29, 1947.)

* From the Bureau of Preventable Diseases, New York City Department of Health, New York, N. Y.

The initial lesion has been observed on practically all parts of the body; it probably represents the site of entry of infection. It was seen in about 95 per cent of the patients examined by us.

2. *Onset.* The onset of acute symptoms is sudden and occurs about four to seven days after the beginning of the initial lesion. The characteristic symptoms are fever, chills or chilly sensations, sweats, headache, backache, lassitude and photophobia. The fever frequently reaches 103 or 104°F., with morning remissions and usually persists, with the other symptoms, for about a week. Chills or chilly sensations and sweats may recur two or three times a day for the first few days. After about a week the fever defervesces and the other symptoms abate.

3. *Rash.* The rash appears on the same day or even several days after the onset of acute symptoms. (Fig. 3.) The lesions resemble the initial lesion but are usually smaller. They are at first maculopapular but later become vesicular; the vesicles dry and the scabs ultimately fall off without scar formation. The lesions are discrete and generalized except that they are seen only rarely on the palms and soles. They may be abundant, moderate or scanty in number. Lesions have been observed on the tongue and palate. The duration is about a week. After the scab has fallen off a brownish discoloration of the skin may persist for several days. No subjective symptoms accompany the rash.

Except for the triad of symptoms just discussed there are no unusual physical signs. Pulse usually follows the course of the fever, respirations are normal and heart and lungs appear normal on physical examination as well as by x-ray. Occasionally the spleen is enlarged; lymphadenopathy is uncommon. There have been no complications and no deaths.

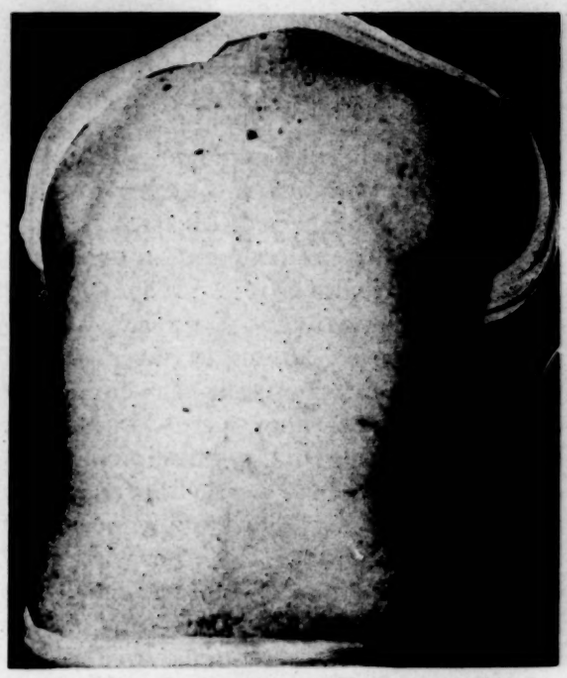


FIG. 3. Rash of rickettsialpox. (GREENBERG, PELLITTERI, KLEIN and HUEBNER. *J. A. M. A.*, March 29, 1947.)

LABORATORY FINDINGS

The usual laboratory determinations were essentially negative except for moderate leukopenia during the febrile period which returned to normal as a rule about two to three weeks after onset of the acute illness. Urine examinations occasionally showed transient albuminuria at the height of fever. Sedimentation rates were slightly elevated, red blood counts were normal and blood cultures were sterile. In the patients in whom chemical determinations of the blood were made, normal cholesterol, sugar, nonprotein nitrogen and chlorides were found and the icteric index was not elevated. Total serum protein and albumin-globulin ratio were also found to be normal. There was no change in the blood pressure nor in the electrocardiogram. Serologic reactions were negative for brucellosis, tularemia, typhoid, paratyphoid A and B and leptospirosis. The Weil-Felix reaction with Bacillus proteus OX19, OX2 and OXK was negative during the convalescent as well as acute stage of the disease, except occasionally in insignificant titers;[2] the heterophile antibody reaction was likewise negative. The complement fixation reactions of the blood serum were negative for syphilis, psittacosis, murine, epidemic and scrub typhus and Q fever. A few sera were tested by Dr. Herald Cox for

African tick fever and were also found negative.

EPIDEMIOLOGY

The original epidemiologic study was made in the borough of Queens in New York City by the New York City Department of Health in cooperation with the U. S. Public Health Service.[3] The epidemic was sharply localized to a group of sixty-nine three-storied houses in three oblong blocks, each block consisting of twenty-three connected houses. They were occupied by 483 families with a total population of about 2,000, of whom 600 were children under fifteen years of age. During the period of study, July to October, 1946, 124 cases were found, an incidence of 6.2 per cent. The rate was 5.3 per cent in children and 6.5 per cent in adults, about equally divided between the sexes. The first cases were reported by physicians practicing in the neighborhood who thought the illness might be atypical chickenpox, a mild form of spotted fever, a form of Brill's disease or some new syndrome. As our studies progressed and the findings were passed on to them the significance of the various features of the clinical picture became manifest.[4]

It was realized early in the study that age, sex and occupation bore no relationship to incidence of disease. It was also obvious that the disease had not been imported since almost all residents had lived in the same apartments for several years and with rare exceptions none of the ill individuals had been away from the city for more than a month preceding onset of illness. Food as a source of infection was also eliminated since no meals were eaten in common by the ill individuals and food supplies were obtained from the same shops by ill and well alike. All milk used was pasteurized and the water supply came from the New York City system. The plumbing was in excellent sanitary condition and there was no evidence of recent breakdown. Examination of water samples indicated no contamination.

Sanitary inspection of the involved houses and the surrounding neighborhood yielded meager results. The vacant lots were clean, shrubbery and seeded areas were well kept and no garbage or other objectionable matter was found. Two stables and two dog kennels in the vicinity were also found to be clean and well kept. Dogs belonging to residents of the development as well as those in the kennels were free of ticks as was the shrubbery in the housing development and in the vacant lots. The only insects seen were common house flies and dog fleas. In spite of a heavy precipitation only one mosquito breeding impoundment was found in the basement of an unfinished house near the development. Larvae were found in this water and the adults were collected from the ceiling of the basement; they were identified as Culex pipiens by Dr. Alan Stone of the U. S. National Museum. Adults of the same species were also found in the basements of the houses under investigation and tests showed them to be non-infectious.

Preliminary epidemiologic investigations pointed to the houses themselves as the site of the source of infection. The only factor common to all the patients was the presence of field or house mice in the houses and surrounding courtyards. All the tenants were aware of their presence. They were seen in the basements, in apartments, in the courtyards and were heard scampering up and down the walls. Dead mice were found in courtyards, basements and apartments. Mouse droppings were found everywhere, including the floors, tables and beds. The possibility that the mice played a part in transmission of the disease suggested itself and a decision was reached to trap them and comb them for parasites. A field laboratory was set up in one of the buildings and traps were set out in many places. In the meantime mites were found in mouse harborages and on incinerator walls (in the basements) by Mr. Charles Pomeranz. After the mice were trapped and combed similar mites were recovered as ectoparasites. They were identified as Allodermanyssus sanguineus (Hirst) by E. W. Baker of the Bureau of Entomology and

Plant Quarantine of the U. S. Department of Agriculture.

A systematic collection of mites from walls, mouse nests and trapped mice was begun in the buildings by means of a suction apparatus. Entry was not obtained in nine of the houses but a search was made in the remaining sixty. An attempt was made to correlate the cases of illness with the presence of mites in the houses of residence. In forty-one houses no mites were found and in these houses there were forty-two cases of illness, an incidence of one patient per house. On the other hand mites were found in nineteen of the houses and sixty-seven cases were reported in these houses, an incidence of 3.5 patients per house. Furthermore, there appeared to be a rough correlation between the number of cases reported from a house and the quantity of mites found there. In each of two houses in which mites were found in large numbers eight cases of illness as compared with an average of 3.5 cases were observed. Multiple cases in a family were not unusual, four cases occurring in each of four families, three cases each in seven, and two cases each in twenty families. None of the sick individuals recalled being bitten by mites or observing them on their bodies, but that is not surprising in view of the smallness of the mite, its absence of color before engorgement and its ready destruction by the rubbing of a finger. One should keep in mind that individuals rarely remember the bite of a tick, an arthropod many times larger than a mite. That the mites found in the buildings were blood sucking was readily observed when they engorged after attaching to mice; furthermore, smears made from those that were found engorged showed mammalian erythrocytes. Although mites were not observed in the apartments by the residents, several housewives in whose families cases were reported had observed tiny blood spots on the bed sheets.

Epidemiologically, a case could be made out against the mites which were apparently infected. How they were introduced into the buildings was a matter of conjecture. However, once introduced they survived and propagated by obtaining blood meals from the mouse which served as a reservoir. When introduced accidentally into the apartments, they readily infected humans by a bite or possibly by the rubbing in of their feces, causing a primary lesion at the site. Propagation of the virus in the human host caused the acute symptoms and rash. To prove this hypothesis it was necessary to recover the infecting virus from the vector, the reservoir and the human host.

PATHOLOGY

Since all patients have survived, examination of pathologic material is limited to biopsies of skin lesions and of a regional lymph node.[5] The skin lesions showed aggregations of small and large mononuclear cells around the blood vessels, especially near sebacous glands. The capillaries showed swelling of the endothelium which bulged into the lumen almost obstructing it. Strands of fibrin were seen in the lumen of some superficial capillaries. Mast cells were observed among the cells forming the perivascular collections, around hair shafts, some sweat glands and occasionally in the derma. In the lymph node there was marked hyperplasia of the reticulum cells in the cortex. The small blood vessels appeared narrowed; they were lined with tall, cuboidal epithelial cells. Numerous mast cells and few eosinophiles were seen. In none of the sections were rickettsial-like bodies observed. However, the pathologic picture resembled that seen in typhus fever and Rocky Mountain spotted fever.

ETIOLOGY

While the epidemiologic studies were in progress, blood specimens were obtained from a number of the patients in the acute stage of the disease and injected intraperitoneally into mice and guinea pigs.[6] Illness in the mice was characterized nine days later by inactivity, rapid breathing and ruffled fur. Pathologically, the mice showed enlarged lymph nodes, a large

edematous liver and a tremendously enlarged and engorged spleen. Suspensions of liver and spleen were passed serially in mice and always produced the same symptoms and pathologic conditions. In guinea pigs the suspension caused scrotal swellings and fever in three to four days. Suspensions of brain from the original mouse were injected into other mice and caused symptoms but no deaths. Brain removed from one of the sick mice on the twelfth day after inoculation was inoculated in a saline suspension into the yolk sacs of embryonated eggs. In a week the embryos were moribund or dead. Films made from the yolk sacs showed numerous intracellular and extracellular diplobacilli which stained well by Machiavello's method but poorly with methylene blue. Yolk sac suspension grew well when passed in other eggs and caused illness in mice and guinea pigs similar to that caused by the animal passage material. It was not possible to cultivate it on acellular media.

The recovered organism was tested by the complement fixation reaction against serums from normal humans as well as of recovered patients, and from patients with Rocky Mountain spotted fever, endemic typhus, tsutsugamushi and Q fevers and syphilis. There was a high degree of specificity except for cross reactions with Rocky Mountain spotted fever. Serums from recovered patients gave positive results in high titers. When blood was obtained early and later in the disease, significant rises in titer were demonstrated. The same serums tested against Rocky Mountain spotted fever antigen gave positive results in about 80 per cent of the cases, usually in a lower titer, but when tested against the antigens of psittacosis, epidemic and endemic typhus, tsutsugamushi and Q and Colorado tick fevers the results were negative.

The Weil-Felix tests with Proteus OX19, OX2 and OXK performed with the serums of recovered patients were negative or occasionally positive in insignificant titers. the name rickettsialpox was given to the disease since it is characterized clinically by the appearance of pocks and is caused by a rickettsia.

Organisms identical with those obtained from human patients were recovered from six pools of mites collected in the buildings under investigation.[7] The mites were ground up and injected intraperitoneally into adult male guinea pigs. Fever and scrotal swelling were observed on the fourth day. Tunica washings caused similar illness in other guinea pigs and characteristic illness in mice. In chick embryos they caused death on the seventh day after yolk sac inoculation and smears from the yolk sac stained by Machiavello's method showed intra- and extracellular red diplobacilli similar to rickettsiae. When these organisms were used as antigen in the complement fixation test with normal human serum and with convalescent guinea pig serum of endemic typhus, Q fever, Rocky Mountain spotted fever and rickettsialpox, positive reactions were obtained with the last two only, a result similar to that obtained with rickettsialpox antigen. Furthermore, guinea pigs convalescent from rickettsialpox were immune to the mite strain.

Flat mites obtained from some of the buildings were allowed to engorge on a laboratory mouse. Ten days later the mouse became ill. Its brain was removed and a saline suspension injected into embryonated eggs. In seven days the embryos died and smears from the yolk sacs showed numerous rickettsiae. Antigens from these yolk sacs gave complement fixation reactions similar to those obtained with the human and with the other mite strains. The name Rickettsia akari was given to the agent recovered from humans and mites.

The recovery of R. akari from mice trapped in the buildings was accomplished last.[8] Saline suspensions of liver and spleen from the trapped mice were injected intraperitoneally into groups of laboratory mice. Nine days later they showed characteristic illness. Passage to mice and guinea pigs was accomplished with suspensions of tissue of the sacrificed mice. R. akari was recovered from the tissues of both the mice and guinea

pigs, and growth in egg yolk sac was obtained with tunica washings of the latter. Cross immunity was demonstrated among the human, mite and mouse strains.

DIFFERENTIAL DIAGNOSIS

Rickettsialpox bears a certain resemblance to several other diseases from which it should be differentiated:

Chickenpox. This is the disease with which it has been most frequently confused because of the occurrence of vesicular lesions in both diseases. However, in chickenpox the entire papule becomes a vesicle so that in a certain stage of the disease only vesicles are seen on the body. They are thin walled and easily broken. In Rickettsialpox the papular element of the lesions remains throughout, the vesicles surmounting the papules. No initial lesion is seen in chickenpox and the fever does not precede the rash. Also, adults are uncommonly affected which is not true of rickettsialpox. Finally, the complement fixation reaction is specific for the latter.

Smallpox. This is a more serious disease. Headache and backache precede the onset of fever, symptoms are more severe, the rash becomes pustular and lasts much longer than in rickettsialpox, there is no initial lesion and mortality is high.

Infectious Mononucleosis. A rash is only an occasional feature in this disease. The blood picture is characteristic and the heterophile reaction is usually positive. Finally, the specific complement fixation reaction in rickettsialpox should distinguish the two diseases.

Other Rickettsial Diseases. (1) *Rocky Mountain spotted fever:* There is usually a history of a tick bite, the rash is macular, papular or petechial, not vesicular, there is no initial lesion and the symptoms are more severe with a fairly high mortality rate. Furthermore, leukopenia is not characteristic and the Weil-Felix reaction is usually positive with Proteus OX19 and OX2.

(2) *Epidemic typhus:* There is usually a history of infestation with lice. Patients are sicker and frequently die. There is no initial lesion and the rash is not vesicular. The Weil-Felix reaction with Proteus OX19 is positive and the complement fixation reaction is specific.

(3) *Endemic typhus:* This disease resembles rickettsialpox in its comparative mildness. However, the rash is macular or papular and occasionally petechial but not vesicular and no primary lesion is noted. The Weil-Felix reaction with Proteus OX19 is regularly positive and the complement fixation reaction is specific.

(4) *Tsutsugamushi fever or scrub typhus:* There is an initial lesion in this disease as in rickettsialpox. The rash, however, resembles that of typhus fever rather than rickettsialpox, the symptoms are more severe and mortality is high. The Weil-Felix reaction is positive with Proteus OXK and the complement fixation reaction is specific.

(5) *Boutonneuse fever:* There is a considerable resemblance between this disease and rickettsialpox. Both are mild diseases with no mortality and in both there is an initial lesion. However, in boutonneuse fever the rash is not vesicular and it is frequently seen on the soles and palms. History of a tick bite and association with dogs is common and the behavior of the organism in laboratory animals is different in the two diseases.[6] Finally, the Weil-Felix reaction with OX19 and OXK is usually positive during convalescence from boutonneuse fever.

INCUBATION PERIOD

Incubation period of the disease, the period between the bite by the acarid and occurrence of the initial lesion, was difficult to determine because none of the patients recalled being bitten and almost all had lived in the same house for a long period of time. In one case, however, a woman visited her sick daughter for one day only and then returned home. She observed an initial lesion a week after the visit. One of the investigators came from Montana to the epidemic area and developed an initial lesion fifteen days later; his incubation

period was, therefore, not more than about two weeks. Another patient had been away on vacation and developed a primary lesion fifteen days after her return; here, too, the incubation period could not have been more than two weeks. One individual living in the epidemic area went out of town and developed an initial lesion six days after departure; the incubation period could, therefore, not have been less than six days. From the meager data one can say that the incubation period appears to be between one and two weeks.

TREATMENT

Rickettsialpox is a self-limited disease and the acute symptoms usually do not last more than a week. No complications or deaths have been reported. Specific therapy, such as para-aminobenzoic acid, has not been tried since the symptoms yield readily to ordinary antipyretic and sedative measures.

ENDEMIC FOCI IN NEW YORK CITY

Reports of suspected cases in New York City occurring in locations removed from the epidemic area soon were reported and investigation was made of all of them.[9] During the second half of 1946, 178 cases, and in the first eight months of 1947, 79 cases were seen in four boroughs of the city. No cases have been reported from Staten Island nor has any authenticated case been reported outside of the city. It is interesting that in the borough of Queens, aside from the epidemic area, only five cases have been seen at a considerable distance from and apparently unrelated to the epidemic. In Brooklyn, the largest borough in the city, only seven unrelated cases have been reported. Most of the cases have occurred on the island of Manhattan and in the adjacent borough of the Bronx, seventy-three in the former and thirty-three in the latter.

Inspection of the spot map of the city indicates that although the cases are widespread they tend to group. Thus in Manhattan no cases have been reported so far in the lower tip of the island. There is also a free area just above and to the east of Central Park. On the other hand, there is considerable grouping in the lower east side and the lower west side, a less concentrated grouping east and west of Central Park and scattered groups on the west side above the park. In the Bronx five cases are spotted in one house in the upper west region, and several groups are seen in the lower middle and west part of the borough. One case has been reported from a small island just off the Bronx. In Brooklyn there is no close grouping but almost all the cases have been reported from the northwestern part of the borough; in Queens, aside from the epidemic area, only five cases have been reported, four in the northwestern part of the borough not too far removed from the Brooklyn cases and one from the opposite part of the borough.

Multiple cases in the same house occurred regularly in the epidemic area in Queens. Multiple cases in the same house have also been reported in Manhattan and the Bronx. In the latter borough five patients were seen in each of two houses; in one of these houses seven more patients were observed by a physician in the building but were not seen by us. In two other houses two patients were seen in each and a probable third patient in one of them. In Manhattan, too, two patients were seen in each of several houses.

With numerous foci spread all over the city, it appears improbable that the disease appeared *de novo* in 1946 in Queens. It is more probable that the disease existed for some time in an unrecognized form and that it was introduced accidentally into the Queens housing area. The conditions being ripe there an epidemic occurred which because of its extent forced itself to the attention of the medical profession. Had only a few cases occurred they would have been diagnosed as chickenpox or some other entity and the disease would have continued to be unrecognized until some other fortuitous occurrence focused attention upon it.

CONTROL MEASURES

Control measures differ little from those used in the control of rodents causing other diseases, such as murine typhus. A preliminary survey is needed to determine the extent of infection in mice. This can probably be accomplished by the systematic trapping of mice and the testing of their blood for the presence of complement fixing antibodies against rickettsialpox. Such tests were positive in mice trapped in the epidemic area in Queens and in houses where cases had occurred in Manhattan and the Bronx. They were negative in laboratory mice and in those trapped outside of New York City.[8] After the endemic foci have been mapped out antirodent measures can be carried out, such as baiting, trapping and poisoning and the elimination of rodent harborages. The use of DDT in the destruction of Allodermanyssus sanguineus has not yet been tried.

VECTOR

Allodermanyssus sanguineus (Hirst) is a small, colorless mite whose body measures about 1½ mm. in length in the female and about one-half that in the male. When engorged, it swells to many times its size and becomes bright red in color. Although first described in a publication in the United States in 1913 by Stanley Hirst,[10] specimens were received by the Division of Insect Identification of the U. S. Department of Agriculture from the District of Columbia in 1909. Another occurrence of the mite in the United States was recorded by the division between 1909 and 1938. From 1938 to 1946 a number of samples were identified. They came from Tucson, Ariz., the District of Columbia, New York City, Philadelphia, Indianapolis and Boston. Most specimens were found in houses or apartments but some were found on humans.[7] Hirst's original description of the mites was from specimens recovered in Egypt.[10] Previous to 1946 there is no record of this mite as a vector of disease.

RESERVOIR

The small house or field mouse is the only animal that has so far been implicated as the reservoir. Mice were found in abundance in all the houses in which cases of rickettsialpox were investigated, and mites were found as ectoparasites of the mice in the epidemic area in which trapping and combing were carried out systematically. Hirst's description of the mite is from specimens found as ectoparasites on Mus rattus, Arvicanthis niloticus and Acomys cahirinus in Assiut, El Hasaiba, Deirut and Kaus in Egypt.

SUMMARY

Evidence has been presented of the occurrence of a newly recognized disease, rickettsialpox, in New York City which occurred in epidemic form in a localized community in the summer of 1946 and has been occurring endemically since. Clinically, it is characterized by the appearance of a painless initial lesion on some part of the body, followed in about a week by an acute onset with fever, headache, backache and other symptoms and by a generalized papulovesicular rash. Routine laboratory examinations are negative except for leukopenia. The disease is caused by R. akari and is transmitted by a mite, Allodermanyssus sanguineus (Hirst), the reservoir for which is the house or field mouse. The organism has been recovered from the blood of patients, from the mites and from infected mice. Serums of recovered patients give a negative Weil-Felix reaction but a positive complement fixation reaction for rickettsialpox. The disease is self-limited and the treatment is symptomatic. No deaths have been reported.

REFERENCES

1. Greenberg, Morris, Pellitteri, Ottavio, Klein, Irving F. and Huebner, Robert J. Rickettsialpox—a newly recognized rickettsial disease. II. Clinical observations. *J. A. M. A.*, 133: 901–906, 1947.
2. Greenberg, Morris and Pellitteri, Ottavio. Rickettsialpox. *Bull. New York Acad. Med.*, 23: 338–351, 1947.

3. GREENBERG, MORRIS, PELLITTERI, OTTAVIO and JELLISON, WILLIAM L. Rickettsialpox—a newly recognized rickettsial disease. III. Epidemiology. *Am. J. Pub. Health*, 37: 860–868, 1947.
4. SUSSMAN, LEON N. Kew Gardens' spotted fever. *New York Med.*, 2: 27–28, 1946.
SHANKMAN, BENJAMIN. Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City. *New York State J. Med.*, 46: 2156–2159, 1946.
5. DOLGOPOL, VERA B. Histologic changes in rickettsialpox. *Am. J. Path.*, 24: 119–133, 1948.
6. HUEBNER, ROBERT J., STAMPS, PEGGY and ARMSTRONG, CHARLES. Rickettsialpox, a newly recognized rickettsial disease. I. Isolation of the etiological agent. *Pub. Health Rep.*, 61: 1604–1614, 1946.
7. HUEBNER, ROBERT J., JELLISON, WILLIAM L. and POMERANTZ, CHARLES. Rickettsialpox, a newly recognized rickettsial disease. IV. Isolation of a rickettsia, apparently identical with the causative agent of rickettsialpox for *Allodermanyssus sanguineus*, a rodent mite. *Pub. Health Rep.*, 61: 1677–1682, 1946.
8. HUEBNER, ROBERT J., JELLISON, WILLIAM L. and ARMSTRONG, CHARLES. Rickettsialpox, a newly recognized rickettsial disease. V. Recovery of *Rickettsia akari* from a house mouse (*Mus musculus*). *Pub. Health Rep.*, 62: 777–780, 1947.
9. GREENBERG, MORRIS. Endemic features of rickettsialpox. *New York State J. Med.*, 48: 502–506, 1948.
10. HIRST, STANLEY. On the parasitic acari found on the species of rodents frequenting human habitations in Egypt. *Bull. Ent. Research*, 5: 225–229, 1914.

Seminars on Hypertension

Consideration of Human Hypertension with Respect to Its Renal Origin and Therapy*

WILLIAM GOLDRING, M.D.
New York, New York

THE Seminars on Hypertension which have appeared in the American Journal of Medicine have emphasized the numerous technics and varied points of view concerned with this problem. Some of the papers have been purely descriptive, others have speculated on the pathogenesis of experimental renal hypertension and human essential hypertension and some have presented data on various types of medical and surgical treatment for human hypertension. It would be expected from the tentative nature of present information concerning hypertensive disease that a number of controversial issues would be raised. These issues have been fairly presented by the various authors with a statement of their personal preferences in each instance.

It is the purpose of this paper to restate some of the controversial issues for further appraisal. It is obvious, of course, that such reappraisal is no more than a statement of agreement or disagreement of another group of observers who make no claim to finality in any of their opinions.

In deciding on the papers to be selected for this summary the purely descriptive studies were omitted since nothing could be accomplished but recapitulation, and the studies dealing with the pathogenesis of hypertension were omitted because of the lack of sufficiently definitive data on which to take even a tentative stand at this time. There remain for the purposes of this discussion those studies dealing with the similarity between experimental renal and human hypertension and those dealing with the treatment of human hypertension.

SIMILARITY BETWEEN EXPERIMENTAL RENAL HYPERTENSION AND HUMAN HYPERTENSION

The demonstration by Goldblatt and his associates that partial constriction of the renal arteries of an animal leads to persistent diastolic and systolic hypertension opened a new field for investigation of human hypertension.[1] One problem in man appeared to be partly clarified, i.e., the probability that the mechanism of hypertension in primary bilateral intrinsic renal disease might arise from the kidneys, even though this assumption still leaves the exact pathogenesis of elevated blood pressure in doubt. The observation of Goldblatt and associates has contributed little to understanding of the etiology of human essential hypertension and it is not yet established that fundamental disturbances in the experimental animal and in the human are identical in nature.

As pointed out by Dexter,[2] in spite of numerous studies, there is as yet no unequivocal explanation of the mechanism of experimental renal hypertension, and no more than a small beginning has been made in uncovering the pathogenesis of human essential hypertension.

In the first paper of these seminars Goldblatt[3] presented evidence for and against the similarity of mechanism in experimental renal hypertension and human essential

* From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

hypertension; the net of his evidence spoke for a striking similarity. On the other hand, Goldring, Chasis and Smith[4] found the evidence for similarity in mechanism was unconvincing. They stated, "If it is predicated that alteration in renal hemodynamics is the primary disturbance underlying essential hypertension, the factors giving rise to this alteration must be sought in anatomical faults affecting some greater or lesser fraction of the renal circulation. Such anatomical faults are not, as a rule, distributed symmetrically, and would not, except in rare instances, alter renal hemodynamics symmetrically." Nevertheless, among twenty-one unselected hypertensive patients studied by us, alteration of renal hemodynamics was identical in the two kidneys; not a single patient showed unilateral renal impairment.[5] This circumstance is compatible only with the view that the underlying cause of the disturbance in renal circulation operates equally in both kidneys. It is difficult to see how this could be the case if alteration in renal hemodynamics *per se* is the primary factor.

Diminished renal blood flow is a common accompaniment of essential hypertension in man. Present evidence, however, indicates that this renal circulatory alteration is not the primary and presumably the initiating factor, but rather a secondary effect resulting from the action of a humoral pressor agent of unknown origin.[6]

It can be accepted that experimental renal hypertension has its counterpart in some forms of unilateral and intrinsic bilateral renal disease in man, but this renal type of hypertension appears to be relatively infrequent, accounting for probably no more than 10 per cent of the incidence of hypertension in adults. The occurrence of some instances of renal hypertension must not lead us into accepting renal origin as the universal rule.

The incidence of hypertension in patients with urologic disease is no greater than in the general population without urologic disease. Friedman, Moschkowitz and Marrus[7] found an incidence of hypertension of 21.8 per cent in 193 patients with unilateral renal disease proven at operation while in a control group of 1,006 living patients the incidence of hypertension was 22.8 per cent. Oppenheimer, Klemperer and Moschkowitz[8] found a 27.5 per cent incidence of hypertension in seventy-nine necropsied patients with unilateral renal disease while in 333 control necropsies the incidence of hypertension was 24 per cent. Baggenstoss and Barker[9] similarly found an identical incidence of hypertension in patients with and without unilateral renal disease (29.3 per cent and 29.0 per cent, respectively) while Braasch, Walters and Hammer[10] found an 18.7 per cent incidence of hypertension in 1,684 living patients requiring renal surgery, a figure essentially identical with the incidence of hypertension in 175 living controls (20 per cent). Last, Crabtree and Chaset[11] found only a 9 per cent incidence of hypertension in 150 patients who had been subjected to nephrectomy for unilateral renal disease.

If it is assumed, as some do, that renal vascular disease, structural or functional, is the primary cause of the development of human essential hypertension and, in the causal sense, precedes all other manifestations of the disease, then admission that vascular disease precedes hypertension leaves the mechanism of the vascular disease unexplained and the etiology of hypertensive disease still unknown. Moreover, sclerosis of the renal arterioles is not invariable early in the course of hypertensive disease. Indeed, admitting the validity of their conclusion, Castleman and Smithwick[12] report that it is absent or minimal in about one-half the patients on whom they had biopsy studies. It seems hazardous to us to base conclusions regarding etiology, pathogenesis or therapy in man on the assumption that the single hemodynamic alteration of elevated blood pressure in the experimental animal is analogous to the disease as it occurs in man.

Human hypertensive disease is a complex disorder of which elevated blood pressure is merely one manifestation. Production of

elevated blood pressure in the experimental animal cannot be construed as evidence of the production of hypertensive disease, nor can the assumption be accepted that when blood pressure is elevated the animal has developed the counterpart of the human disease, nor that when blood pressure is lowered to normal levels by presumably specific antipressor agents the animal is cured of the disease. The hypotensive action of such substances as renal extract in experimental renal hypertension cannot be accepted as evidence of specific cure since several investigators admit that the actual causative agent or agents of experimental renal hypertension is still unknown.

The general picture is such that we see no reason for modifying our position as summarized by one of us (H. W. S.)[13] "To read the rapidly expanding literature on this subject is only to discover the complexity of the problem of ultimate etiology. One observer holds that hypertension is of dietary origin, while another relates it to climate, both interpretations being far from negligible, since the incidence of the disease is remarkably low among many primitive peoples. By other observers, it is contended that there is a distinct hereditary trend, at least in predisposition, while correlations with endocrine imbalance are not lacking. At the other extreme, the psychoanalyst tells us that the early fluctuating phase of essential hypertension is a manifestation of a psychoneurosis based on excessive and inhibited hostile impulses; and again, that inhibition of heterosexuality or repression by a dominant parent, with chronic, hostile, but unsuccessful, rebellion against submissiveness, are common psychological features of the disease.

"In the present state of our knowledge, it would be hazardous to advance the kidneys as more than one contributor to a malignant mélange, which, if we are to accept a fraction of the evidence, is a constitutional disorder involving in addition to the kidneys, the vascular bed, the vasomotor centers, the cerebral cortex, perhaps the entire organism and its genetic foundations. And yet, considering the tentative nature of most of the suggestions which have been made in regard to etiology, it is unnecessary to magnify them.

"When and if it can be demonstrated that the relief of altered renal hemodynamics specifically abolishes all signs of hypertensive disease in man, then the major link in the chain of logic which incriminates the kidneys will be complete. This is asking that we reach our desideratio summa, the cure or prevention of the disease, at the beginning of our problem, which is perhaps more than we can expect, but short of this demonstration, it is impossible to charge the kidneys with the sole responsibility in human hypertensive disease."

TREATMENT

In no other disease have so many therapeutic procedures been conceived, tried and discarded. This circumstance is understandable in view of its great prevalence and potentialities for ultimate harm, a circumstance which instills desperation in both patient and doctor. The history of therapy in hypertensive disease is replete with instances of unwarranted enthusiasms and baseless claims. Unfortunately the period of unwarranted enthusiasms and baseless claims has not passed and is not likely to pass until discovery of the ultimate cause or causes.

Perhaps the most important single obstacle to a clear interpretation of the effect of a therapeutic procedure is the complete reliance on the level of the blood pressure, a measurement so crude and variable as to be almost wholly without value as a guide to therapeutic effectiveness. The best that can be said for the blood pressure level is that it is a consistent sign of hypertensive disease and that its measurement is easily available. It seems clear that the measurement of a more fundamental and less variable manifestation of the disease is urgently needed for evaluation of therapeutic effect. This limitation introduces a considerable hazard in the assessment of any type of therapy for hypertension. It is a

further fact that morbidity and mortality in hypertensive disease are directly due to vascular disease. Treatment which lowers blood pressure, therefore, is beneficial only in the view that vascular disease is a consequence of the blood pressure level. However, the relationship between hypertension and vascular disease is not fully understood. Until this relationship is clarified the rationale for therapeutic measures in hypertension designed solely to lower blood pressure cannot be accepted without question.

Richard Bright established the first fact, i.e., that obstruction of blood flow through the kidneys precedes and accounts for hypertension, which in the absence of blood pressure measurement at that time was expressed as cardiac hypertrophy. Further observation by other investigators uncovered instances of prolonged hypertension in which at necropsy the vascular involvement of the kidneys was clearly insufficient to result in significant obstruction to blood flow. From this observation arose the second thesis, i.e., hypertension was due to functional vasoconstriction and renal and splanchnic vascular disease is a consequence of the elevated blood pressure. More recently a third point of view has been introduced suggesting that elevation of blood pressure and vascular disease are concomitant effects of an unknown mechanism and independent of each other. The evidence to support each of these three contentions is circumstantial and as yet it is not possible to have full confidence in any.* Consequently, present day treatments using lowering of blood pressure as the guide must be considered empirical.

LOW SALT DIET IN THE TREATMENT OF HYPERTENSION

A diet containing less than 200 mg. of sodium has been suggested for the treatment of human essential hypertension. In the past few years it has been applied extensively.

The rationale of the sodium restricted diet is far from clear. However, its proponents adhere to the thesis that the adrenal cortex is involved in the genesis of essential hypertension. They point to two principal lines of evidence suggesting disturbance of sodium metabolism: one is that the blood sodium to chloride ratio is higher in hypertensives than in normotensives and the other is that on a rigid twenty-four-hour sodium chloride restriction, normotensive subjects lose weight and develop diuresis whereas hypertensive patients do not. Other investigators have been unable to confirm these observations.

Even admitting the possibility of participation of the adrenal in the genesis of hypertension, it seems clear that modification of a secondary effect, namely, abnormal sodium retention could not be expected to correct a primary underlying adrenal cortical disturbance. Sodium restriction, therefore, resolves itself into another treatment designed to lower blood pressure without regard to its underlying cause and, therefore, is a treatment of doubtful value.

While some of the earlier studies have indicated an occasional significant effect of this diet on the blood pressure level, more recent reports have been decidedly disappointing. The more one takes into account the great variability of the blood pressure level and the more insistence is placed on a prolonged and adequate control period, the more obvious it appears that a sodium restricted diet does not significantly lower blood pressure.

In connection with the practical application of the sodium restricted diet and even allowing for apparent moderate diminution of blood pressure in some patients, Perera[14] makes the following statement: "There is nothing to suggest that the small changes in resting blood pressure associated with rigid sodium chloride withdrawal are of therapeutic significance or that prolonged restriction will exert any influence on the natural history of this disorder (hypertensive disease)." This reviewer is in full accord with the attitude as expressed and

* The single exception in this controversy applies to primary bilateral renal diseases as glomerulonephritis, pyelonephritis and polycystic renal disease in which it is generally believed that renal disease precedes and accounts for hypertension.

finds it most refreshing at a time when the literature is filled with enthusiastic overstatements concerning treatment of a disease about which so little is known.

RICE DIET IN THE TREATMENT OF HYPERTENSION

Among the numerous theories advanced to explain the pathogenesis of hypertension, one is concerned with failure of deamination. The final breakdown of amino acids is brought about by two separate processes: decarboxylation which can occur in the absence of oxygen and deamination which requires the presence of oxygen. Failure of deamination, therefore, would permit amines to enter the systemic circulation and since many amines are known to be pressor in their action hypertension could result. It is clear from these facts that failure of deamination could occur as a result of a deficiency of aminase, the action of an inadequate aminase or as a result of the action of normal aminase in the absence of adequate available oxygen. Since there is no known means to improve or increase amine oxidase activity and no means to make more oxygen available in the kidneys, the alternative is to decrease quantitatively the amount of amino acid which reaches the kidneys and other tissues in which deamination is known to occur. It should be stated at this point that beyond inference, disturbances of renal metabolism have not as yet been shown to be involved in the pathogenesis of human hypertension.

The rationale of the rice diet in the treatment of hypertensive disease is an extension of this general thesis. In an early report Kempner[15] proposed the following as a working hypothesis: "If for the moment we disregard the renal excretory function and consider the kidney only as an organ of metabolism, we can assume, as a basis for experimental approach, that pathological conditions in the kidney may lead to the following changes:

"a) Substances which are normally removed by the kidney cell metabolism may increase in amount in the blood or tissue fluids.

"b) Substances which are normally produced by the kidney cell metabolism may decrease in amount.

"c) Some of the substances normally metabolized by the kidney cells may be metabolized vicariously by the liver cells, with a resulting increase in the metabolic products of the liver cells.

"d) 'Abnormal' substances may appear in blood or tissue fluids which under physiological conditions exist only in an intermediary, non-apparent phase of the kidney cell metabolism since normally they are immediately further metabolized to harmless end products.

"If we assume that some of these 'abnormal' substances which appear when the metabolic function of the kidney cells is disturbed are harmful and play a role either directly or indirectly in the development of hypertension, vascular retinopathy, encephalopathy, heart lesions and new kidney disease, the working hypothesis suggests itself; that the ordinary mixed diet may contain constituents which increase the production of these 'abnormal' harmful substances by the diseased kidney cells."

Kempner[16] further states that the experimental basis for application of the rice diet in treatment of human hypertension rests on "observations made on the protein, fat and carbohydrate metabolism of isolated kidney cells under various pathological conditions (cell injury and/or changes in pH, sodium bicarbonate concentration, oxygen tension and metabolizable substrate)."

The rice diet contains 300 Gm. of rice. The protein content of the diet is 20 Gm.; fat 5 Gm.; sodium 150 mg.; chloride 200 mg. and carbohydrate in sufficient amount to bring the total caloric value of the diet to 2,000; supplementary vitamins are added. The carbohydrates are taken in the form of fruit juices and sugar. Fluid intake is limited to 1 L. a day. Balance studies on patients taking the rice diet indicate that they are in nitrogen balance in spite of the apparently low protein intake. As a rule,

there is an initial weight loss of about 10 pounds during the first week of this diet after which the patient maintains his weight. This diet has been tried extensively on hypertensive patients since its introduction in 1944. It has aroused a great deal of interest and discussion, reminiscent of the initial attitude toward all forms of therapy which have so far been introduced in the treatment of hypertension in man.

Opinions in regard to the effectiveness of the rice diet have varied from brilliant to insignificant. There have been a few equivocal reports, but most of these investigators have attributed the moderate falls in blood pressure which they observed to the low sodium content rather than to the low protein content or any other specific character of the rice diet. The use of low sodium intake in the treatment of hypertension has been discussed under another heading.

In reviewing the various studies it is a striking fact that the most favorable study of all was conducted without regard to the establishment of adequate pretreatment control levels for blood pressure whereas in the unfavorable studies such a control was rigidly applied before institution of the rice diet. Even the most casual contact with hypertensive patients over a period of time makes it clear that when such a rigid control of the blood pressure level is lacking it is quite impossible to assess intelligently any fall in blood pressure on any form of therapy. It is quite apparent to those who see the need for a control period prior to treatment that it often takes two weeks and occasionally as long as six weeks in a hospital environment before the blood pressure becomes sufficiently stabilized to permit introduction of a new variable in the form of treatment. If one includes only those studies in which this control period has been properly carried out, it can be stated without equivocation that the rice diet has no effect on the level of the blood pressure.

However, proponents of the rice diet in the treatment of hypertension point to the astonishing incidence of reversal of the so-called "hypertension pattern" of the electrocardiogram toward normal, diminution of the size of the heart and regression of papilledema. It is these objective evidences of the effect of the rice diet which are urgently in need of explanation. Regression of these objective evidences of hypertensive disease even when the blood pressure level has not been lowered either suggests correctness of the hypothesis that elevated blood pressure is a concomitant disorder and unrelated to the presence or progression of vascular disease, or that we do not as yet fully appreciate the enormous potentiality for spontaneous variation in the untreated hypertensive patient.

However, these striking data come from the one source which has reported brilliant results with the rice diet treatment[15] and as yet there has been no confirmation from other observers. Until such confirmation is available, the rice diet does not warrant any more than casual interest.

SURGICAL TREATMENT OF HYPERTENSION

Unilateral Nephrectomy. It has been amply demonstrated in the experimental animal that partial constriction of the main renal arteries to both kidneys invariably results in persistent elevation of systolic and diastolic blood pressures. However, observations on the blood pressure-raising effect of unilateral renal artery clamping are meager. Such data as are available indicate that persistent blood pressure elevation commonly follows unilateral constriction in the rat, but the frequency of spontaneous bilateral renal disease in this experimental animal leaves considerable doubt as to the validity of this observation. The few observations that are available on the effect of unilateral renal artery constriction in the dog indicate that increase of the blood pressure is quite uncommon and only transient. While there are reported instances of persistent elevation of blood pressure in the dog after unilateral renal artery constriction, they are exceptional; even more

exceptional is the demonstration that such blood pressure returns to normal upon removal of the operated kidney some months after constriction. In view of the rarity of persistent hypertension following unilateral renal artery constriction in the dog and the infrequency of cure in these following nephrectomy, acceptance of unilateral renal artery constriction as a mechanism in the pathogenesis of even experimental renal hypertension would appear to be hazardous and certainly offers little or no basis for transferring this mechanism and cure to human essential hypertension. Yet these meager and inconclusive observations supply the rationale for nephrectomy in hypertensive man.

It would be supposed that if unilateral renal disease can initiate hypertension in man, the incidence of hypertension would be greater in patients with unilateral renal disease than in a control group of normal subjects. However, available statistical evidence clearly indicates that the incidence of hypertension is similar in both groups. In 585 published instances of various unilateral renal diseases the incidence of hypertension was 24.2 per cent; in 433 necropsy controls the incidence of hypertension was 26.5 per cent and in 2,928 living controls the incidence of hypertension was 26 per cent.[17]

In his recent and detailed analysis of all available data bearing on the incidence of hypertension in unilateral and bilateral urologic diseases, Smith[18] stated, "to conclude on the basis of the above data that perhaps as many as 10 per cent of hypertensives have demonstrable urologic abnormalities of such a nature as to lead to functional impairment (and the figure 10 per cent seems generous in view of the data of Ratliff, Bechgaard, Pearman, Braasch and their co-workers), is no warrant for inferring that in these 10 per cent the urologic disease is responsible for the hypertension. The probability of coincidence is very great. At the present time the only way a causal relationship can be demonstrated in any particular case is by curing the hypertension by removing the offending organ." However, despite the lack of an acceptable experimental basis and failure of convincing statistical support from observations in man apparent cures have been reported. Even when strict criteria are demanded, Smith[18] has pointed to 47 cases of 242 reported operations which must be accepted as instances of apparent cure. His requirements for "successful" unilateral nephrectomy included the establishment of persistent preoperative hypertension with adequate control of the blood pressure level, fall of the blood pressure into the normal range promptly after the operation and persistence in the normal range for one year or more.

While these patients must be considered probable cures, the variable and often unpredictable course of the blood pressure level is of such magnitude that acceptance of this therapeutic procedure must for the present remain tentative. In spite of these rare but apparently successful instances, enthusiasm for unilateral nephrectomy in the treatment of hypertension is distinctly on the wane, and even its strongest proponents are emphatic in stating that decision to remove a kidney should rest altogether on the urologic indications and not upon the hope of removing the cause of hypertension; before nephrectomy is performed the diseased kidney should be shown to be practically devoid of function and the opposite kidney free of disease.

Sympathectomy. The rationale of sympathectomy rests on the concept that so-called essential hypertension begins as a functional vasoconstrictive disease mediated through the sympathetic nervous system. In this view hypertension is the initial clinical evidence of the disease and arteriolar sclerosis is a direct result of the elevated pressure. Surgical interruption of these pathways, therefore, would in theory prevent vasoconstriction, hypertension and arteriolar sclerosis. It would appear, then, that the rationale for sympathectomy rests upon arbitrary selection of one of the three current hypotheses previously mentioned

concerning the interrelationship between hypertension and vascular disease.

After observations on about 6,000 sympathectomized patients by numerous observers opinions vary from insignificant to brilliant results. The ideal patient for sympathectomy has been characterized as the early labile hypertensive by some and the late hypertensive with advanced vascular disease by others of equal experience with this form of treatment. After many attempts it is generally agreed that no satisfactory preoperative guide exists which might be helpful in anticipating the effect of sympathectomy. The wide differences of opinion in regard to the value of this treatment rest upon the unpredictable natural history of the disease in any single individual. Conclusive opinion is further made difficult by dependence on a comparison of blood pressure levels before and after operation, a measurement more unpredictable and undependable as a basis for opinion than any other single evidence of the disease. In short, the extremely variable course of hypertensive disease makes it impossible to obtain a satisfactory control.

However, in spite of these practical objections to easy acceptance of sympathectomy as a useful therapeutic measure it must be admitted that there are occasional instances of what appear to be striking arrest of the disease. Even though such a result is highly exceptional in a large experience, it points clearly to the need for an open mind. Available evidence points strongly to the diverse etiology of so-called essential hypertension and it may well be that a neurogenic mechanism is the sole cause of hypertension in a small number of patients. Unfortunately these individuals cannot be recognized in advance of operation. Even in these rare instances it is not to be assumed that the disease is cured since it is not reasonable, in the present state of our knowledge, that sympathectomy eliminates the still unknown primary mechanism. However, in light of the basic assumption that elevated blood pressure is the sole and direct cause of vascular disease it may be accepted, although without final proof, that prolonged lowering of the blood pressure is of therapeutic value. It should be emphasized again at this point that there is equally valid evidence to support the two alternative opinions, that vascular disease in the kidneys precedes and is independent of the hypertension and that vascular disease and hypertension are independent of each other and are concomitant effects of a still unknown humoral mechanism. If either of these latter hypotheses prove to be correct, it is obvious that reduction of the blood pressure level by sympathectomy can serve no useful purpose.

There can be little question that sympathectomy has a place in the ill defined program of treatment of hypertension, but in view of its tentative rationale it must be regarded as an experiment as yet unfinished. Those who accept sympathectomy with more or less enthusiasm are impressed with mass statistics on longevity or with alterations in specific manifestations of the disease such as relief of symptoms, lowering of blood pressure, diminution of heart size, reversal of abnormalities in the electrocardiogram and regression of papilledema. Mass statistics on longevity may be misleading in a disease with a variable and unpredictable course in which an adequate control is not available.

Relief of symptoms because of their subjective nature cannot with confidence be specifically ascribed to any particular therapy. Furthermore, it is common experience that subjective symptoms may be significantly relieved in patients in whom the blood pressure level is unaffected. The level of the blood pressure is dependent not only on the causative mechanism but upon numerous vasoconstrictor influences unrelated to the basic causative mechanism and subject to spontaneous recession. Thus partial recession of the blood pressure level may be accounted for by prolonged bed rest together with a resigned acceptance of the illness and the reassurance which results from intelligent application of simple psychotherapy. Reduction in size of the heart

cannot be accepted without reservation since in many published reports it is obvious that dilatation and heart failure were present before operation, as indicated by disappearance of x-ray evidences of pulmonary congestion, an effect which is often accomplished by prolonged bed rest alone. Reversal of electrocardiographic changes in the T waves is in the same debatable category since reversal of these changes has been reported after treatment with such apparently unrelated procedures as renal extract, tyrosinase, rice diet, sodium-free diet and after mercurial diuresis. The same reservation applies to papilledema. There are as yet no satisfactory data on the incidence of spontaneous reversal of these manifestations in an untreated control group of hypertensives.

Two patients in our series may be cited as examples of the difficulty in interpreting the results of sympathectomy: The first was a forty-five year old male whose preoperative blood pressure averaged 160/120 mm. Hg. His only preoperative complaint was substernal pain on effort. His preoperative electrocardiogram was normal. Following operation, his usual blood pressure was in the vicinity of 130/70 mm. Hg. He was under observation for eleven months postoperatively. During this period the anginal episodes continued without change and three months after operation he developed episodes of acute left ventricular failure. Repeated electrocardiograms during the period of normal blood pressure showed progressive inversion of the T waves in the first and precordial leads. In the eleventh postoperative month he died suddenly. It seems a fair conclusion from these data that the coronary disease in this instance progressed at the anticipated rate in spite of the absence of elevated blood pressure. The second patient was a thirty-eight year old white male who had established hypertension during a ten-year period of observation. At the time of sympathectomy his blood pressure was in the vicinity of 240/160 mm. Hg. His electrocardiogram showed the so-called hypertension pattern of inverted T waves in the first and precordial leads with depression of the ST segment in lead I. There were fresh hemorrhages in the retinae with well marked blurring of the disc margins. He was in moderate chronic left ventricular failure. Following operation, his blood pressure level remained consistently at about the level of 160/100 mm. Hg. Six months after operation blurring of the discs had completely subsided and the T waves had returned to the upright position. However, one year postoperatively, and in spite of the apparent objective improvement of the blood pressure level, the electrocardiogram and the retinae, the patient developed for the first time repeated episodes of acute left ventricular failure and acute encephalopathy, characterized in various episodes by transient aphasia, hemiparesthesia and acute transient loss of vision. He is still alive four and one-half years after operation. It would appear that this patient, while showing regression in some manifestations of the disease, showed progression in others. One is confronted with obvious difficulty in arriving at a decision as to the usefulness of operation in this instance.

These case histories are cited not because they necessarily help to elucidate the problem but rather to indicate the latitude which is possible in interpretation. One could take the stand that in the first patient the operation was unsuccessful in preventing progress of the coronary disease in spite of normal blood pressure and in the second patient that the effect of sympathectomy cannot be interpreted with confidence; one might make the assumption that both patients lived for a longer period of time than might have been expected without operation. This problem is common and the discrepancies in the conclusions of various studies may well reflect a situation in which the same facts are subjected to different shades of interpretation.

Personal experience with sympathectomy has led us to the conclusion that as yet sympathectomy has not been shown to have

succeeded in significantly altering the course of hypertensive disease. However, there is reason to accept the possibility that if essential hypertension proves to be a disease of diverse etiology, a small segment of the hypertensive population may be materially helped by sympathectomy. It is the possible ultimate isolation of this small group from the large heterogeneous mass of so-called essential hypertensives which should sustain interest in the operation as a highly desirable clinical experiment.

SUMMARY

Good therapeutic effect in essential hypertension has been claimed for such diverse methods as salt restriction on the one hand, and sympathectomy on the other, to say nothing of thiocyanate therapy, psychotherapy and a host of others. Such an attitude toward treatment can lead only to the conclusion that none is adequate. This is quite understandable in view of the fact that the ultimate cause of hypertension is unknown and that all treatment at the present time is purely empirical.

Accepting this then as a fact, we have to define more closely our objective in treating persons with hypertension with our limited information. There appears to be a distinct division of opinion among those who believe that alleviation of subjective symptoms is a desirable objective and those who believe that lowering the level of blood pressure is a more desirable objective. It seems clear that subjective symptoms in hypertensive disease do not, with perhaps few exceptions, depend upon the level of blood pressure since it is a common observation that lowering of the blood pressure level by any means is not necessarily accompanied by alleviation of symptoms and that alleviation of symptoms may occur even when the blood pressure level has not been altered.

The ultimate goal of symptomatic measures is relief of subjective symptoms and while this is frequently accompanied by lowering of the blood pressure level, the latter is of secondary importance. Decline of blood pressure level is not to be interpreted as regression in the underlying cause of the disease, but rather as amelioration of those secondary and reversible factors which are superimposed on the basic causative mechanism.

While relief of subjective symptoms may completely rehabilitate a hypertensive patient, mere lowering of the blood pressure level without relief of symptoms serves no such purpose. This is not to imply that lowered blood pressure is necessarily without some benefit, but rather that it is not to be considered the prime objective of a plan of symptomatic management.

Perhaps the most valuable single device in rehabilitation of the hypertensive patient is psychotherapy; the planned and detailed methods employed by the psychiatrist are not necessarily superior to repeated conferences with a sympathetic physician who will give attention to problems responsible for emotional instability. A physician properly trained in general medicine and with an interest in psychiatry is competent to undertake such treatment and beneficial results are often obtained in a relatively short time. Simple, sympathetic reassurance is often sufficient to relieve disturbing symptoms. The physician can foster this attitude by prolonging the interval between examinations, particularly in the early uncomplicated period when symptoms are few or absent. Psychotherapy intelligently applied often results in dissipation of the anxiety, depression and irritability which accompany the phobia of high blood pressure.

Apart from elimination of the cause of the disease, which is not possible at this time except in rare instances, it would appear that the main objective of treatment should be to retard or prevent development of vascular disease which is the ultimate cause of disability and death. No significant progress has been made in this direction.

It is our present considered opinion that with rare exceptions any treatment based upon the assumption of similarity between experimental and human hypertension is doomed to failure. And, furthermore, that

any treatment directed solely toward temporary reduction of blood pressure is futile. Final treatment will come only when the causative mechanism of human hypertension is discovered and specific measures are devised for its elimination.

Except for the rare instance of pheochromocytoma of the adrenal and the very rare instance of unilateral renal disease, hypertension is not curable. The methods of treatment discussed in this seminar and others not touched upon are merely designed to alter the clinical aspect of hypertensive disease either by eliminating subjective symptoms or by lowering blood pressure. When both can be accomplished, patient and doctor are lulled into a sense of security, but whether or not any of the measures of treatment now at hand actually retard the progress of hypertensive disease is extremely doubtful. In spite of this pessimistic attitude toward present day treatment for hypertension and with full knowledge of what it means to the worried patient and the equally worried doctor, it would appear to be a healthier attitude and more likely to lead to ultimate solution than an attitude of ready acceptance which has the potentiality of engendering a false sense of security.

REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W. Studies on experimental hypertension: 1. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exper. Med.*, 59: 347, 1934.
2. Dexter, Lewis. Mechanisms of human hypertension. *Am. J. Med.*, 4: 279, 1948.
3. Goldblatt, H. Experimental renal hypertension. *Am. J. Med.*, 4: 100, 1948.
4. Goldring, W., Chasis, H. and Smith, H. W. Experimental hypertension. *Spec. Pub. New York Acad. Sc.*, 3: 177–179, 1946.
5. Chasis, H. and Redish J. Function of the separate kidneys in hypertensive subjects. *Arch. Int. Med.*, 70: 738, 1942.
6. Goldring, W., Chasis, H., Ranges, H. and Smith, H. W. Effective renal blood flow in subjects with essential hypertension. *J. Clin. Investigation*, 20: 637, 1941.
7. Friedman, B., Moschkowitz, L. and Marrus, J. Unilateral renal disease and renal vascular changes in relation to hypertension in man. *J. Urol.*, 48: 5, 1942.
8. Oppenheimer, B. S., Klemperer, P. and Moschkowitz, L. Evidence for the Goldblatt mechanism of hypertension in human pathology. *Tr. A. Am. Physicians*, 54: 69, 1939.
9. Baggenstoss, A. H. and Barker, N. W. Unilateral renal atrophy associated with hypertension. *Arch. Path.*, 32: 966, 1941.
10. Braash, J. E., Walters, W. and Hammer, H. J. Hypertension and surgical kidney. *J. A. M. A.*, 115: 1837, 1940.
11. Crabtree, E. G. and Chaset, N. Vascular nephritis and hypertension: combined clinical and clinicopathologic study of 150 nephrectomized patients. *J. A. M. A.*, 115: 1842–1846, 1940.
12. Castleman, B. and Smithwick, R. H. The relation of vascular disease to the hypertensive state based on a study of renal biopsies from 100 hypertensive patients. *J. A. M. A.*, 121: 1256, 1943.
13. Smith, H. W. Studies in the Physiology of the Kidney. Porter Lectures, Series 9. Lawrence, 1939. University of Kansas.
14. Perera, G. A. and Blood, D. W. The relationship of sodium chloride to hypertension. *J. Clin. Investigation*, 26: 1109–1118, 1947.
15. Kempner, W. Compensation of renal metabolic dysfunction; treatment of kidney disease and hypertensive vascular disease with rice diet. *N. Carolina M. J.*, 6: 61, 1945.
16. Kempner, W., Treatment of hypertensive vascular disease with rice diet. *Am. J. Med.*, 4: 545–577, 1948.
17. Goldring, W. and Chasis, H. Hypertension, and Hypertensive Disease. Pp. 105–118. New York. 1944. The Commonwealth Fund.
18. Smith, H. W., Hypertension and urologic disease. *Am. J. Med.*, 4: 724-743, 1948.

Combined Staff Clinics

Congenital Heart Disease

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DICKINSON W. RICHARDS, JR.: This clinic is designed to present both the surgical and physiologic aspects of some of the problems relating to congenital heart disease. Dr. Langmann will initiate the discussion.

DR. ALFRED G. LANGMANN: Although congenital heart diseases, or perhaps more properly congenital anomalies of the heart and great vessels, constitute only about 2 per cent of the total incidence of organic heart disease and about 5 per cent of that encountered in children, they have become a subject of particular interest and importance in recent years. Stimulation of this interest was due largely to the successful ligation by Gross in 1939 of a patent ductus arteriosus in a young girl. Since then operations for the correction or alleviation of three other cardiovascular anomalies have been introduced, viz., coarctation of the aorta, the tetrad of Fallot and 'vascular ring.'

The correct diagnosis of these anomalies which are amenable to surgical operation and of others for which corrective procedures may be devised in the future presents a real challenge, particularly to the clinician, the cardiologist, the physiologist and the roentgenologist. Roentgenograms of the heart taken at different angles and also esophograms have given valuable information about the size of the various chambers of the heart and abnormal partitions of the great vessels. In some medical centers angiocardiography has been found to be of distinct aid in the visualization of septal defects, the pulmonary circulation and the great vessels. Cineroentgenographic study of the heart and great vessels promises to yield even more important data, especially in the province of dynamics. The successful catheterization of the heart, recently carried out even in infants, has furnished information of distinct value in the diagnosis of shunts of various types through the oxygen and blood pressure values so obtained.

Criteria have been set up for the clinical diagnosis of a number of congenital cardiovascular anomalies but it is well to remember that as further anatomic studies are made these criteria may have to be amended. A case in point is the 'machinery' murmur associated with patent ductus arteriosus. This still constitutes the most characteristic feature of the physical findings in this anomaly but is no longer considered a *sine qua non;* for a fair number of patients have been operated upon in whom a patent ductus was found but who before operation had only a systolic murmur although they had other features suggestive of this abnormality.

It is generally stated that about 50 per cent of patients with congenital cardiovascular anomalies have lesions that are clinically insignificant. Accurate anatomic diagnosis is rendered all the more difficult by the fact that in many instances the anomalies are multiple. The most severe of these, often associated with extreme cyanosis, are encountered in early infancy and are compatible with but short life. In the children who survive, every attempt should be made to arrive at as accurate an anatomic diagnosis as possible. Age is an

important factor if surgery is to be considered. It seems to be generally agreed that children tolerate intrathoracic interference better than adults and that they make a quicker recovery after operation. The decision as to whether or not surgical intervention is indicated if symptoms are absent or minimal is a matter that must be decided in each individual case.

DR. RICHARDS: Dr. Humphreys will present the surgical aspects of patent ductus arteriosus.

DR. GEORGE H. HUMPHREYS II: In the past nine years forty-nine patients with the presumptive diagnosis of patent ductus arteriosus have been operated upon at the Columbia-Presbyterian Medical Center. Of these eleven proved to have some other anomaly. Of the thirty-eight patients in whom a patent ductus arteriosus was present, in twenty-six the ductus was uncomplicated by other anomalies or by superimposed infection and was ligated (twenty-two cases) or divided and sutured (four cases) with complete recovery. Four of the twenty-two patients in whom ligation was performed have persistent murmurs which raise the question of recurrent patency although in one case recurrence has been proved by cardiac catheterization not to exist. All four patients in whom the ductus was sutured are free of murmur.

Six of the patients operated upon were suffering or had suffered from subacute bacterial endocarditis. Three had received no penicillin and were actively infected at the time of operation. Two of these are cured and free of murmurs six and five years, respectively, after operation. The third died one month after operation following drainage of a metastatic brain abscess; at autopsy the ductus was closed and the vegetation on the pulmonary artery had healed. One patient was apparently cured by penicillin and his ductus subsequently divided with complete recovery. Two patients developed recurrences; one was cured of both the infection and the recurrence by subsequent ligation and is well and free of murmur six years later; the other was apparently cured of the infection by penicillin; was then re-operated upon and an aneurysm divided and sutured. She is well two years later.

Two additional patients developed recurrence following ligation. One had an aneurysm of the pulmonary artery at the time of ligation and only one ligature was used. Her murmur never disappeared and it is assumed that the ligature cut through. Recurrence with aneurysm occurred in one otherwise uncomplicated case with death a year later following wiring of the aneurysm.

In addition to the two deaths mentioned there were four other patients with patent ductus arteriosus who died after operation. One with an uncomplicated ductus died of hemorrhage on the operating table during an attempt to divide and ligate the ductus, a death which would not have occurred had ligation only been performed. One patient was a middle aged hypertensive in borderline cardiac failure. Operation was done in the hope of relieving her cardiac load but she died in failure three weeks after operation. In one patient the ductus formed part of a more complicated anomaly resulting in a vascular ring around the trachea and esophagus; death from left heart failure followed division of the ductus. The sixth death occurred of circulatory failure on the operating table following exploration only. At autopsy a patent ductus complicated by a large dissecting aneurysm of the pulmonary artery due to subacute bacterial endarteritis was found.

Thus the total mortality of six patients, or 16 per cent, was due largely to complications of the disease. In only two, or 5 per cent, was it due directly to the operation. Thirty-two patients, or 84 per cent, recovered from operation and only one (in whom the operation was technically inadequate) has convincing evidence of persistent patency.

I should like at this point to introduce Miss W., one of our patients who illustrates many points of interest. She is a young lady who has been known to have a cardiac murmur since infancy. During childhood

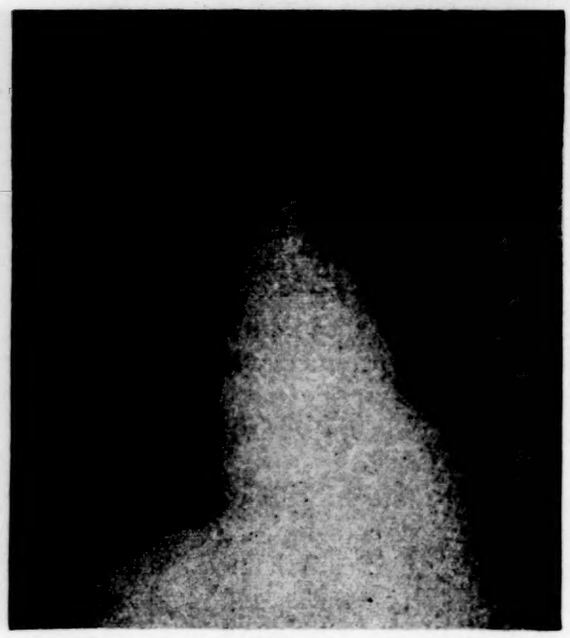


FIG. 1. X-ray of heart of Miss W., with patent ductus arteriosus, showing increase in transverse diameter of heart and prominence in area of pulmonary artery.

an attempt was made to have her restrict her activity because of the murmur but she herself never experienced any inability to carry out normal exercise. She grew and developed at a normal rate. She did not present a feeding problem. She had no abnormalities of growth. In fact she was unusually free of any serious illness.

During her adolescence she was supposed to continue her restrictions but frequently disregarded them and felt no ill effects. For example, when she went to high school she was supposed to take the elevator, but she often climbed four or five flights of stairs without dyspnea. She stated that she had no cardiac symptoms of any kind. Since graduating from high school she has worked in a department store.

I saw her first last summer. She looked much as she does now, a healthy young woman with no cyanosis, no clubbing of fingers or toes and no abnormal pulsations in the nail beds at rest. On the examining table the cardiac pulsation was not unusually strong. There was a slight thrill felt over the base of the heart. A loud, continuous, rough murmur was present and was heard most clearly over the third left interspace. The pulmonic second sound was greatly exaggerated. The murmur was transmitted to the apex of the heart and heard over the aorta posteriorly and over the femoral artery. The blood pressure was 155/53. There was a considerable increase in the pulse pressure but there were no other abnormalities.

She was admitted September 19th and studied by Dr. Baldwin whose findings will be presented later. At the time of her admission her blood pressure was the same as when previously seen. Her hemoglobin was 14 Gm. The red count and the hematocrit were normal. The electrocardiogram was normal except for unusual Q_2 and Q_3 which made Dr. Wégria, who was not informed of the diagnosis, raise the question of a congenital defect. X-ray of the heart (Fig. 1) showed a slightly increased overall diameter of the heart as compared to the normal. There was a slight prominence, not very conspicuous, in the pulmonary area and otherwise very little except for some increase in the bronchovascular markings of the lung.

We believed that with this increase in the heart size, with the high pulse pressure, and particularly after the catheterization studies, her heart was unquestionably carrying a burden from which it could be relieved. She was therefore operated upon on September 27th. A ductus about 1½ cm. long and 1 cm. in diameter was present in its characteristic anatomic position. The pulmonary artery was considerably dilated, more than one would suspect from the x-ray picture, and it overlay the arch of the aorta. The ductus was ligated in continuity with three ligatures of umbilical tape; the thrill disappeared immediately. Her recovery was without complication. The blood pressure rose to 125/90 on the second day postoperatively and then fell gradually to 110/80 where it has remained. She was out of bed on the second day after operation and she went home on the ninth day after operation. During the six weeks after operation she gradually returned to normal activity. She noted no subjective

change in the heart, but when I saw her six weeks later stated that she felt lighter and that her extremities no longer tended to be cold and uncomfortable. It is a common finding that the peripheral circulation is improved in such cases.

Her pulmonic second sound remained somewhat accentuated but there was no murmur whatever. The postoperative x-ray taken at that time showed the prominence in the pulmonic area still present. That is not surprising; when the pulmonary artery has been dilated for many years, it does not shrink immediately. The bronchovascular markings in the lungs were now normal and the transverse diameter of the heart was obviously less.

DR. RICHARDS: Before Dr. Greene gives the measurements in the case of Miss W. I might go over briefly some of the procedures by which we attempt to gain physiologic information in cases of this kind. Actually the measurements that are made are not very many and are quite simple in principle. They involve, of course, catheterization of the right side of the heart, including right auricle, right ventricle and, when possible, the pulmonary artery. Occasionally, if there are defects, the catheter may go into other places. The chief criteria for diagnosis are alterations in oxygen content in one or another of these chambers and alterations in pressures. By means of these measurements the anatomic lesions in a good many instances can be quite well defined.

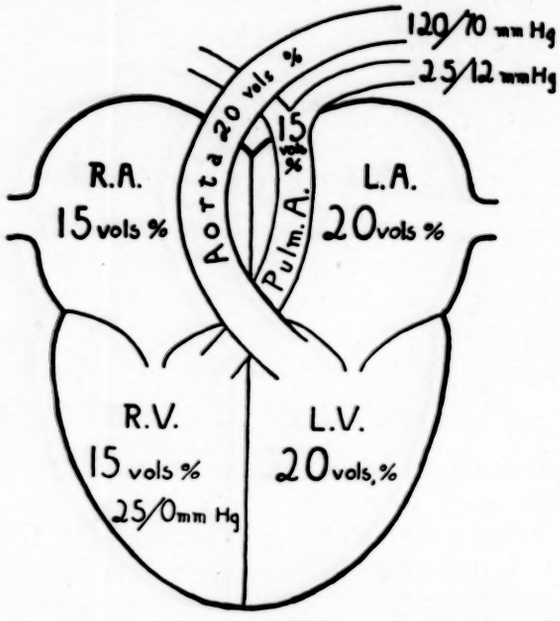
From the point of view of diagnosis the most simple anatomic lesion is that of interventricular septal defect. In this condition oxygenated blood is forced from the left into the right ventricle during cardiac systole. The oxygen content of the right ventricular and pulmonary arterial blood is increased as compared with that of the right auricular blood. The pressure in the right auricle is normal. The right ventricular pressure is increased to a variable extent; it is usually significantly elevated if the septal defect is sufficiently large, by reason of the left ventricular pressure being transmitted, in part, to the right side. If the right ventricular pressure is increased, then that in the pulmonary artery is also increased. These are the findings associated with an interventricular septal defect.

If there is a communication between the aorta and pulmonary artery, then oxygenated blood flows from the aorta into the pulmonary artery and the oxygen saturation is increased in the pulmonary artery. If the pulmonary valve is competent, the right auricular and right ventricular oxygen saturations remain normal. As for the pressures they are not greatly different from those found in interventricular septal defect. The increased flow from the high pressure aorta into the lower pressure pulmonary artery usually increases pulmonary arterial pressure to some extent and the right ventricle must hypertrophy to meet and overcome this increased pulmonary arterial pressure.

In evaluating the phenomenon of increased ventricular or pulmonary arterial pressures there are two factors to be considered: one is that of obstruction and the other is that of increase in flow. In the instances just cited, increase in flow is associated with some increase in pressure. In other conditions, such as pulmonary artery narrowing or stenosis, the increase in pressure occurs with a lessening of flow. It therefore becomes very important to quantitate the actual blood flows in any given case, and that can be done quite readily by the so-called Fick principle. This can be described briefly as follows:

If one obtains (Fig. 2) a figure of 20 volumes per cent of oxygen in the arterial blood by actual measurement, that means that there are 20 cc. of oxygen contained in each 100 cc. of arterial blood. If one obtains from the right auricular (or venous side) a figure of 15 volumes per cent, that means 15 cc. of oxygen per 100 cc. of venous blood. We also measure the total oxygen used by all the tissues in a minute's time. For example, it is 300 cc. per minute; then knowing that for each 100 cc. of blood flowing from the arterial to the venous side

5 cc. of oxygen are taken up by the tissues and that the total oxygen taken up by the whole body in a minute's time is 300 cc., then 300 divided by 5 will give the total number of batches of 100 cc. each of blood flowing from the arterial to the venous side,



$$\text{Pulmonary blood flow} = \frac{300}{20-15} \times 0.1 = 6 \text{ L./min.}$$

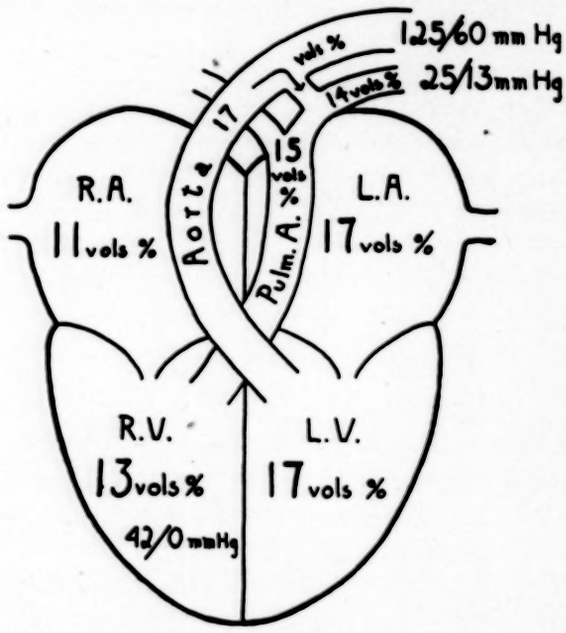
$$\text{Systemic blood flow} = \frac{300}{20-15} \times 0.1 = 6 \text{ L./min.}$$

Arterial saturation at rest = 96%
Arterial saturation after exercise = 96%
Hemoglobin = 15 Gm.
Hematocrit = 45%

FIG. 2. Showing the oxygen saturation and pressure relationships in a normal individual. The blood flow figures are in terms of liters per minute.

or the total systemic blood flow. In this case it would be sixty batches of 100 cc. each, or 6,000 cc. of blood flow per minute. The smaller the oxygen difference from the arterial to the venous side, the less oxygen is taken up by the tissues per unit of blood flowing. That means the faster the blood flow and the greater the total volume flow per minute.

In the lungs the same operation obtains, with the oxygen, of course, going into the blood instead of coming out. But the same principle enables one to measure the total blood flow through the lungs. If one obtains blood from the pulmonary artery and finds, for example, 15 cc. of oxygen per 100 cc. of blood, and in a brachial or femoral artery (which is usually the same as the pulmonary vein) it is 20 cc., that means that 5 cc. are added to each 100 cc. of blood flowing through the lungs. The



$$\text{Pulmonary blood flow} = \frac{240}{17-14} \times 0.1 = 8 \text{ L./min.}$$

$$\text{Systemic blood flow} = \frac{240}{17-11} \times 0.1 = 4 \text{ L./min.}$$

FIG. 3. Illustrating the derangement in oxygen saturation and pressures in Miss W., with patent ductus arteriosus.

pulmonary blood flow in this instance (Fig. 2) would be 6,000 cc. per minute.

With this brief introduction Dr. Greene will give the results in the case just presented by Dr. Humphreys, the case of Miss W.

DR. DAVID G. GREENE: Figure 3 presents the data that we found in studying the first patient. We wanted to know the size of the shunt and thus the resultant extra burden on the heart. As the patient was asymptomatic we hoped that this information would help Dr. Humphreys in making the decision whether or not to operate.

The oxygen content of the mixed venous blood in the right auricle was 11 volumes per cent. The right ventricular blood oxygen content was higher, 13 volumes per cent,

indicating some admixture of arterialized blood in this chamber. At the bifurcation of the pulmonary artery, close to the site of a possible patent ductus, we obtained blood with a still higher oxygen content, 15 volumes per cent, indicating further oxygenation of the right ventricular blood. The catheter tip may have been almost directly in the stream of arterial blood coming from the aorta. Further out in the left pulmonary artery there was a blood oxygen content of 14 volumes per cent, probably a more representative value for the mixed pulmonary artery blood.

We leave for a moment the question of the site of the shunt to calculate its size. We assume that the femoral arterial sample represents the blood in the aorta, the left ventricle, the left auricle and the pulmonary vein. Using this oxygen content, 17 volumes per cent, and the pulmonary artery oxygen content of 14 volumes per cent, we find a pulmonary arteriovenous oxygen difference of 3 volumes per cent. The oxygen consumption measured at the same time was 240 cc. per minute. Dividing the oxygen consumption by the pulmonary arteriovenous difference gives a pulmonary blood flow of 8 liters per minute. Calculating in the same manner but using the femoral artery oxygen content, 17 volumes per cent, and the right auricular mixed venous blood oxygen content, 11 volumes per cent, a systemic arteriovenous difference of 6 volumes per cent is obtained. This value divided into the oxygen consumption per minute gives a systemic blood flow of 4 liters per minute. Therefore, the pulmonary blood flow of this patient is twice her systemic blood flow, an excess circulation which must represent a considerable burden on her heart. Additional evidence of increased cardiac work is the significantly elevated right ventricular systolic pressure of 42 mm. of mercury.

The question of the location of the shunt or shunts cannot be settled from the blood oxygen data alone. In this instance there were two possibilities to be considered: an interventricular septal defect plus a patent ductus, or a patent ductus with regurgitation of oxygenated blood through an incompetent pulmonic valve. The latter interpretation was indicated by the finding of a dilated pulmonary artery at operation and the disappearance of the murmur following surgery. We have encountered pulmonic regurgitation in one other patient who at operation was found to have a patent ductus; however, three other patients with a large ductus had competent pulmonic valves.

DR. RICHARDS: I might say that in resolving the question of pulmonic regurgitation, re-study after operation will sometimes give the answer. If there has been pulmonary regurgitation and the ductus is shut off, with normal relations re-established, the regurgitation will sometimes be overcome, the pulmonary artery will resume its normal size and the pulmonary arterial and right ventricular oxygen will become normal. Whereas if there is a septal defect that is not corrected by operation, some oxygen admixture will persist after operation.

Dr. Cournand has carried out one study in a case of patent ductus arteriosus before and after operation in which this type of admixture did disappear following operation, showing that it was due to pulmonary regurgitation and not to a septal defect.

DOCTOR: You have not catheterized this patient a second time?

DR. RICHARDS: No.

DR. HUMPHREYS: It would be nice if all cases were as simple as that of Miss W. But they are not, and we will try to present not only established and clearcut situations but also those which remain in doubt. In these particularly the surgeon is now following the physiologist and relying on him very heavily to elucidate what is going on and to give him a lead as to what sort of mechanical change might help the patient.

I would like now to present another patient, a child in whom we were not able to get cardiac studies. This child was born in March, 1941, in Sloane Hospital, the second child of American parents. There was a normal delivery and normal background.

He was well developed at birth, had good color, good nutrition and no difficulty in breathing. Unfortunately, his heart was not examined before he was discharged at the age of ten days. He re-appeared six months later, referred back by the Health Clinic because of bronchitis, failure to gain weight and 'blue spells' associated with crying. Examination in the clinic showed poor nutrition, cardiac enlargement and a low pitched systolic murmur over the precordium, maximal at the left sternal border. X-ray confirmed the cardiac enlargement and showed some congestion in the lungs. He was followed closely in the clinic. It was thought that no cardiac diagnosis could be made although the question of patent ductus arteriosus was raised. During the six months he gained only 1 pound and at the end of a year weighed 11 pounds. He was eating poorly, had an almost constant cough and respiratory difficulty. X-ray at one year revealed that the heart had increased in size in the intervening six months and now showed a clearcut bulge in the region of the pulmonary artery.

With this finding, and in spite of the fact that the murmur was still systolic and in spite of the fact also that the child was in very poor shape, it was believed that a diagnosis of patent ductus was sufficiently well founded to warrant operation; it was thought furthermore that his poor progress was such that he would very likely die if nothing were done and that the risk of operation should be taken.

At operation on April 9, 1942, a large ductus was found and doubly ligated after entering the pericardium. Postoperatively his condition was poor for the first week, with both circulatory and respiratory symptoms. He had a definite pneumonia which was helped by sulfadiazine but he then developed a sulfadiazine reaction; the drug had to be stopped whereupon the pneumonia recurred, but eventually his temperature returned to normal and by the end of the second week his condition already appeared better than before operation. He remained in the hospital for sixty-one days and during this period he made such a rapid improvement in weight and strength that his weight on discharge was 19 pounds, almost twice his admission weight.

After removal of the dressing a persistent, soft systolic murmur was heard over the apex and on discharge this murmur had increased in its area to include the whole left border of the heart. This, of course, immediately raised the question as to whether the ductus had been completely occluded, whether one of the ligatures had cut through, or whether he had some other anomaly. He has been followed now for five years after the operation. This murmur has been consistently present. It has varied in intensity from visit to visit, at times being quite rough and accompanied by a thrill, at other times (as at present) much softer and located lower over the heart.

During the first two years weight and growth gain were spectacularly good. During this period his cardiac shadow improved and his electrocardiogram, which before operation had shown not only left preponderance but also inverted T waves suggesting myocardial damage, returned to normal. His x-ray pictures in 1943 (at the age of one and one-half years) and in September, 1944 and the spring of 1945 have changed very little; they are still abnormal. The heart is more to the left than it should be. There is still a prominence in the pulmonic area although not as pronounced as preoperatively. On the other hand his pulmonary fields are much better than before operation. Recently his weight gain has slowed down. He has had a number of infections. He appears less well than he did two years ago although he is growing normally. In December of last year, for the first time, definite cyanosis and slight clubbing were noted in the clinic. The question arises as to whether this child with his persistent murmur (not recurrent, he has never been free of a murmur) and with these findings does not also have other difficulties.

The third case (G. G.) is that of a child in whom cyanosis was noted at the age of two months. At two years he suffered a

fractured skull following which he developed a hemiplegia which has left some residual weakness. His growth and development, however, were not delayed. His nutrition was reasonably good, although not excellent, but by the time he was four or five years old he began to develop exertional dyspnea which became more pronounced as he grew and attempted more exercise. After exercise cyanosis became more prominent; at rest it was much less but still noticeable.

He was admitted to Babies Hospital on March 8, 1946, at the age of eleven years. He showed definite cyanosis of the lips and nail beds with marked clubbing of fingers and toes. There was a slight residual weakness of the extremities on the right. Heart examination showed some bulging of the precordium with no visible pulsation, thrill or shock. There was no enlargement of the heart to percussion, the sounds were regular and of good quality. A loud, harsh murmur was heard throughout systole in the aortic area transmitted throughout the precordium but not to the back.

X-ray (Fig. 4) revealed a small cardiac silhouette and large hilar shadows with approximately normal bronchovascular markings. This picture is not typical of pulmonic stenosis, which is characterized by a marked defect in the area of the pulmonary artery, diminished or faint vascular markings and a rising of the apex of the heart above the diaphragm.

This child was operated upon in May, 1946. The end of the right subclavian artery was anastomosed to the side of the small right pulmonary artery by suture. This is the operation described by Blalock. It has, as you see, formed a surgical patent ductus. In other words, we created in this child what we eliminated in the other patients. He made an uncomplicated recovery and was allowed up after the third day.

Before operation his hemoglobin was 19 Gm. with a red count of 11,500,000. The hematocrit was 66, an increase of 40 per cent. Three months after operation his hemoglobin had fallen to 13 Gm. and his

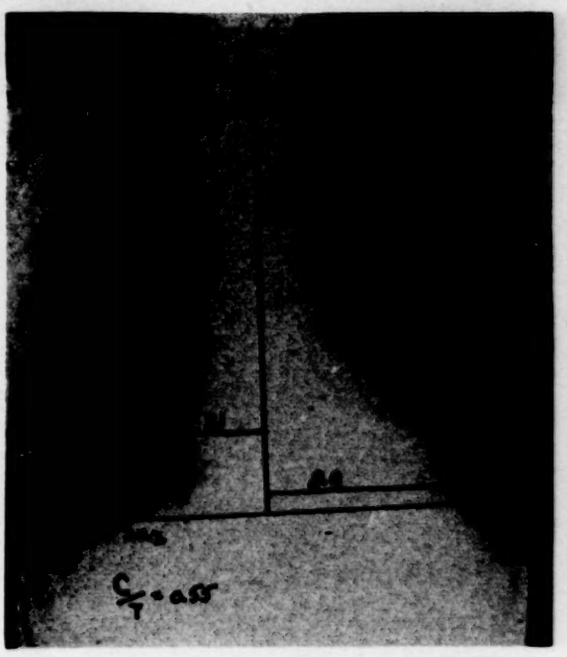


FIG. 4. Preoperative x-ray of the heart in G. G. The transverse diameter is not increased.

red count to 5,800,000. His arterial saturation before operation was 72 per cent at rest. Three months after operation it was 89 per cent. This child went home after the second week and during the next three months he did extremely well. His cyanosis became imperceptible and it no longer appeared on exercise. In fact he rejoiced in his ability to exercise to the point that when he returned to school in the fall he joined the football team and played very vigorously.

On November 5th he was re-admitted to the hospital following attacks of vomiting, headache and low grade fever which had begun about four weeks previously. This worried us because of the possibility of subacute bacterial endocarditis. Especially was that in mind since examination at that time showed him as you see him now, with no obvious cyanosis but with some clubbing still persisting although now very largely disappeared.

At that time his heart (Fig. 5) was greatly enlarged and overactive. The loud, rough systolic murmur was still present and in addition there was a continuous murmur in the operative area. His hemoglobin on admission was 13.5, the red count 5,000,000

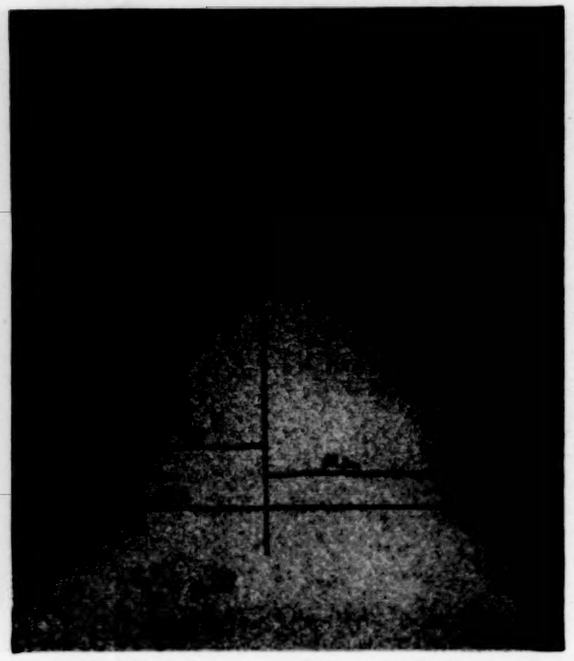


FIG. 5. Postoperative x-ray of heart in G. G. showing marked increase in size following the surgical establishment of a patent ductus equivalent.

MOTHER: He has headaches but they last only a day and then are gone. He has no more diarrhea, no more vomiting or fever.

DR. HUMPHREYS: He is still able to get around pretty well?

MOTHER: He does everything.

DR. HUMPHREYS: Thank you very much.

DR. RICHARDS: This patient has been studied and followed very carefully by Dr. Baldwin. Would you tell us about your work, Dr. Baldwin?

DR. ELEANOR DEFOREST BALDWIN: The diagnosis of pulmonic stenosis can be made by passing a catheter into the right ventricle and pulmonary artery and measuring the pressures. In the right ventricle the systolic pressure is greatly elevated while in the pulmonary artery beyond the stenotic area the pressure is low and the pulse pressure small. This is well demonstrated in pressure tracings from a patient with the tetrad of Fallot. (Fig. 6.) The pulmonary artery pressure is only 19/10. On withdrawal of the catheter tip into the right ventricle a much higher pressure, 102/3, is immediately recorded. As frequently happens with this maneuver there are a few abnormal contractions as the catheter tip enters the ventricle.

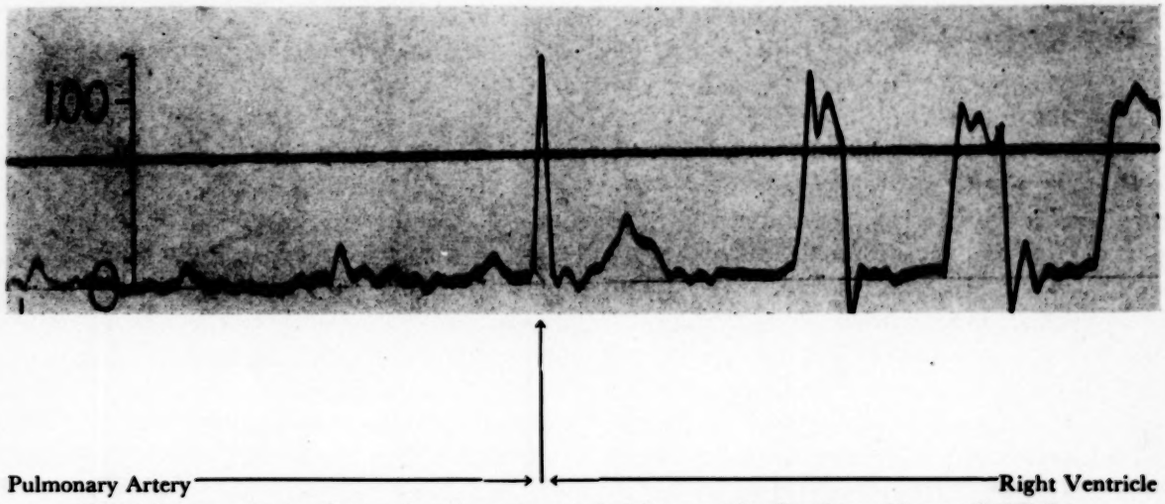


FIG. 6. Pressure tracing from pulmonary artery and right ventricle of patient with tetrad of Fallot.

and the oxygen saturation 88 per cent. His electrocardiogram showed an increase in the P-R interval but otherwise it was not changed. His blood cultures were repeatedly negative. His fever after a week of irregular elevation dropped to normal without any antibiotic treatment and after a week he was allowed to go home. Since that time how has he been?

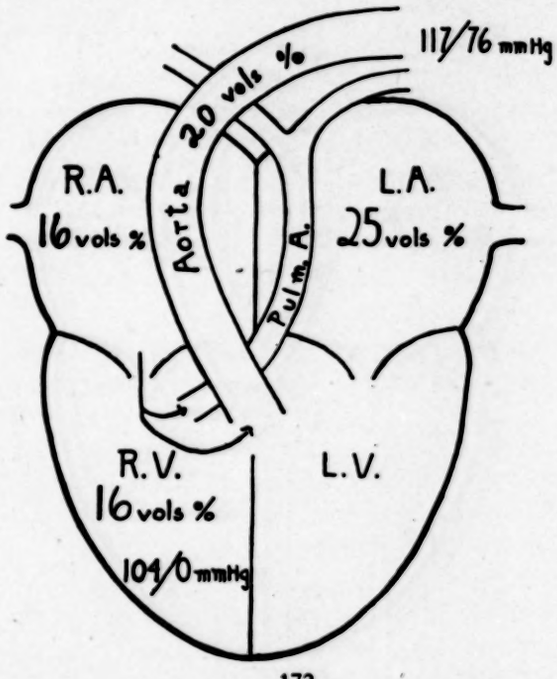
MOTHER: Fine.

DR. HUMPHREYS: He has not had any more attacks?

In case G. G., just presented by Dr. Humphreys, observations made during catheterization of the right heart are typical of the physiologic changes found in cases of

interventricular septal defect associated with pulmonic stenosis: (1) The systolic pressure measured in the right ventricle is very high, approximately that of the peripheral arterial system. In this case (Fig. 7) the right ventricular systolic pressure was 104 mm. of mercury, corresponding closely to the systolic pressure of 117 which was obtained simultaneously in the femoral artery. (2) The pulmonary blood flow is considerably less than the systemic blood flow as calculated by the Fick formula from the minute oxygen consumption and oxygen arteriovenous differences.

We have direct measurements from which we may calculate the systemic blood flow. Using these figures, we find that the oxygen arteriovenous difference between the aorta and right auricle is 20 minus 16, or 4 volumes per cent. The minute oxygen consumption of this patient during the blood sampling was 172 cc. The systemic blood flow is 172 divided by 4, or 4.3 liters per minute. Since we did not obtain the oxygen content of either the pulmonary artery or vein, certain assumptions must be made to estimate these values. The pulmonary vein and left auricular blood oxygen content is taken to be 25 volumes per cent with a 96 per cent oxygen saturation. This figure is chosen because we have found that blood obtained directly from the pulmonary vein in patients with interauricular septal defects has an oxygen saturation between 94 and 96 per cent; and our assumption is therefore valid if pulmonary function is normal and blood is aerated well in flowing through the lungs. If we assume further that the pulmonary artery contains blood similar in oxygen content to that in the right ventricle, the pulmonary oxygen arteriovenous difference is 25 minus 16, or 9 volumes per cent, which divided into the oxygen consumption of 172 cc. gives us a pulmonary blood flow of only 1.9 liters. However, as we will show in the next case, the pulmonary artery may receive systemic blood from a patent ductus or bronchial arterial anastomosis. If only such blood were circulating through the lungs, the pulmonary arteriovenous difference would be 25 minus 20, or 5 volumes per cent, and the pulmonary blood flow 3.4 liters. This maximum for pulmonary blood flow is still less than the systemic blood flow. Since the pulmonary blood flow is mechanically limited by the stenosis, the volume of blood flowing through the shunt would be expected to increase under conditions which augment the volume of blood returning to the right heart. A measure of the extent of this increase is the profound drop of arterial oxygen saturation, from 75 to 45 per cent, observed in this patient following the very mild exercise of walking up and down a step twenty times during one minute.



$$\text{Pulmonary blood flow} = \frac{172}{25-16} \times 0.1 = 1.9 \text{ L./min.}$$

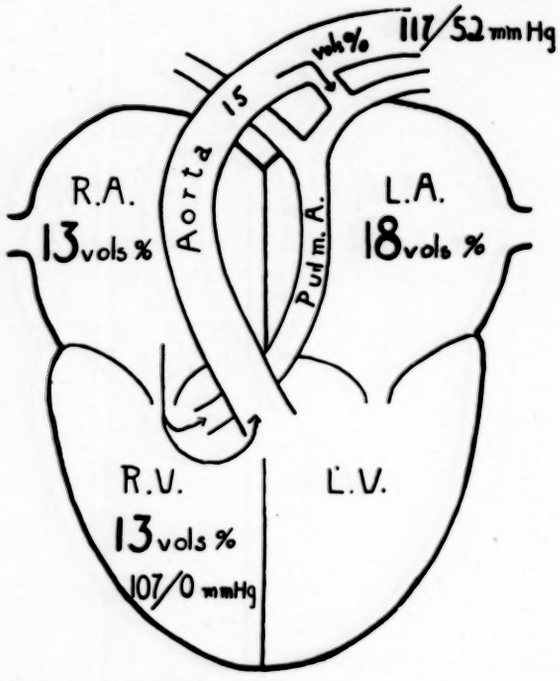
$$\text{Systemic blood flow} = \frac{172}{20-16} \times 0.1 = 4.3 \text{ L./min.}$$

Arterial saturation at rest = 75%
Arterial saturation after exercise = 45%
Hemoglobin = 19 Gm.
Hematocrit = 66%

FIG. 7. Indicating the abnormal findings in G. G. before operation. These represent the tetrad of Fallot.

Following his operation, during which the subclavian artery was anastomosed to the pulmonary artery, we repeated our

studies. (Fig. 8.) The right ventricular systolic pressure was found to be unchanged, 107/0 mm. of mercury. The femoral arterial pressures were 117/52 mm. of mercury; the systolic identical with that observed before operation, the diastolic lower by 20 mm.



Pulmonary blood flow = ?

Systemic blood flow $= \frac{168}{15-13} \times 0.1 = 8.4$ L./min.

Arterial saturation at rest = 86%
Hemoglobin = 13.4 Gm.

FIG. 8. Postoperative findings in G. G. To the tetrad of Fallot has been added a patent ductus.

of mercury. (It is of interest that the pulse pressure increased in this subject in whom an arteriovenous fistula was created, whereas it decreased in the preceding patient following the ligation of the patent ductus.) The oxygen contents of the right auricular and ventricular bloods are again identical with one another, 13 volumes per cent, representing an oxygen saturation of 75 per cent. The blood leaving his left ventricle has an oxygen content of 15 volumes per cent and an oxygen saturation of 86 per cent. His systemic oxygen arteriovenous difference is 2 volumes per cent. Since his minute oxygen consumption is unchanged from the preoperative value of 172 cc., the systemic blood flow is 8.4 liters a minute. The catheter could not be passed into the pulmonary artery so it was impossible to measure the pulmonary blood flow. Nonetheless, the rise of the resting arterial saturation to 86 per cent indicates that there is a greatly increased flow of blood through the artificial patent ductus.

Obviously the operation has not changed the dynamics within the right ventricle; the pulmonic stenosis and right to left shunt into the over-riding aorta exist as before. However, the additional blood flow through the lungs by way of the anastomosis increases the volume of arterialized blood returning to the left heart, raising the saturation of the blood leaving the left ventricle from 75 to 86 per cent. This means that there has been an increase of the oxygen tension in the arterial blood from 39 to 86 mm. of mercury. The saturation of the mixed venous blood is now 75 per cent, which is identical with the saturation of his preoperative arterial blood. The larger amount of oxygen available to the tissues of the body accounts for this boy's spectacular improvement following operation.

The increased systemic blood flow observed postoperatively raises an interesting question. The identical oxygen consumption measured during the two procedures eliminates an increase in the metabolic demands of the body as a cause. An increase in the cardiac output is the common finding in cases of arteriovenous shunts elsewhere in the body and is considered to be a compensating mechanism. The decreased viscosity of the blood of this patient, as evidenced by the drop of his hematocrit from 66 per cent to normal values, may in addition contribute to the postoperative increase of his systemic blood flow.

DR. ANDRÉ COURNAND: We have seen a case which was quite similar to this one before operation, in which we could demonstrate definitely a shunt from the right to the left on slight exercise.

DR. RICHARDS: Are there other questions?

DR. ROBERT F. LOEB: I should like to ask about left ventricular hypertrophy in

this boy. It is obvious that what we do in this operation of Blalock's is to induce an anomaly which we rectify in people who do not have worse trouble. The question that has been in my mind is: how long will it be before we find that these patients, who have been relieved of cyanosis and have improved function temporarily, run into difficulties such as are encountered with any large functioning patent ductus? This child has developed definite cardiac hypertrophy and I should like to know how often this occurs. How long a period of time elapses before it does occur?

DR. RICHARDS: The 8.4 liters per minute indicates a real increase in the systemic blood flow. When venous communication occurs suddenly from traumatic causes, cardiac hypertrophy develops quite rapidly if the communication is large.

DR. HUMPHREYS: X-rays of this boy showed a good deal of cardiac dilatation. It should be emphasized that he had overexerted himself. He is a good case to show because he does bring up exactly the point made by Dr. Loeb. We are creating in these children all the liabilities which we are eliminating in such patients as we showed first. This child does have an increased load on the heart and does have as much, maybe more, risk of bacterial infection. That risk is one which is considered worth while taking for the sake of the immediate relief, which is very dramatic.

DR. JOHN CAFFEY: In our roentgenologic follow-up studies, this boy is the only patient who has shown cardiac enlargement following operation. We have four other good follow-ups and there has not been even a transitory dilatation of the heart. It is not part of the operation but something in this patient.

DR. BALDWIN: A factor in this may be that several of the patients have had a hemiplegia. This patient felt so well on being suddenly released that he overexerted himself.

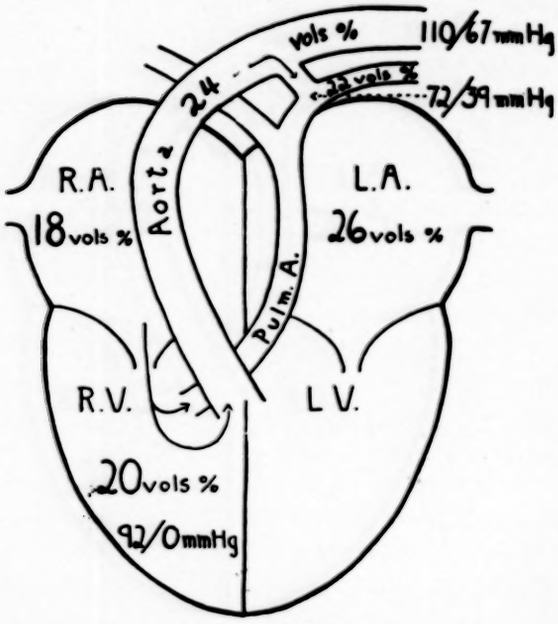
DR. RUSTIN MCINTOSH: I would like to ask about the postoperative regimen in that connection. It is customary to let children with malformation of the heart find their own level of exercise tolerance. Do you believe it would have made any difference at all if his exercise had been restricted by directives following operation, or do you think that it is a case of six of one and half a dozen of the other and let him go and play football?

DR. RICHARDS: I think a certain amount of protection would be a good thing. I do not know how others feel about this point.

DR. MCINTOSH: One could argue that it is a question of the speed of development. The same change can be effected, that is, the same degree of cardiac dilatation and hypertrophy might be reached at a later time if the daily exertion were less.

DR. BALDWIN: The next case (D. F.) shows the importance of catheterizing the pulmonary artery whenever possible to avoid missing important anomalies. He is a twenty-two year old Bermudan who has been blue since birth. His growth was slow and his activity somewhat limited. He was, however, able to ride a bycicle, an important activity in Bermuda, and in recent years has worked as a barber. For twelve months before his trip to the States he suffered a series of hemoptyses, two of which were alarming and during which he is said to have lost at least 1 pint of blood. On arrival here he denied extreme limitations of his activity. He was able to climb two flights of stairs slowly but not rapidly. He was cyanotic with marked clubbing of the fingers and toes. His heart was enlarged, both to the right and to the left. A loud systolic murmur was heard in the tricuspid area, a snapping second sound in the pulmonic area. X-ray of his heart presented a uniform cardiac enlargement with an increase of the pulmonary conus and a rather diffuse increase of the vascular shadows throughout the lung fields. During our first study (Fig. 9) we found hypertension in the right ventricle of 92/0 mm. of mercury, associated with a peripheral systemic blood pressure of 110/67. The oxygen content of his right auricular blood was 18 volumes per cent and that of his

right ventricle 20 volumes per cent. At the time of this study we explained this difference of oxygen contents by the assumption that during certain phases of the cardiac cycle there was a small amount of arterialized blood flowing from left to right through



$$\text{Pulmonary blood flow} = \frac{190}{26-22} \times 0.1 = 4.8 \text{ L./min.}$$

$$\text{Systemic blood flow} = \frac{190}{24-18} \times 0.1 = 3.2 \text{ L./min.}$$

Arterial saturation at rest = 86%
Arterial saturation after exercise = 60%
Hemoglobin = 21 Gm.
Hematocrit = 74%

FIG. 9. Summarizing the relationships in D. F. Compare with Figure 7.

the ventricular septal defect. We were unable to pass the catheter into the pulmonary artery. The oxygen content of his femoral arterial blood was 24 volumes per cent, an oxygen saturation of 86 per cent; following our standard mild exercise, the oxygen saturation of the arterial blood dropped to 60 per cent. We repeated our right heart catheterization studies and were successful in passing the catheter into the left pulmonary artery as you can see from this x-ray. (Fig. 10.) During these studies we were able to obtain blood samples from the right auricle, ventricle and pulmonary artery. We found an oxygen content of 18 volumes per cent in the right auricle, 20 volumes per cent in the right ventricle, 22 volumes per cent in the pulmonary artery and 24 volumes per cent in the femoral artery. We must again assume an oxygen content of 26 volumes per cent for the blood returning from the lungs to the left heart. By subtracting the oxygen content of his pulmonary arterial blood from that assumed for the pulmonary vein blood we obtain a pulmonary arteriovenous oxygen difference of 4 volumes per cent which divided into the minute oxygen intake of 190 cc. gives us a pulmonary blood flow of 4.8 liters per minute. Similarly, the systemic blood flow is calculated by using the oxygen difference between the femoral arterial and right auricular bloods, 24 minus 18, a difference of 6 volumes per cent. When divided into the oxygen intake of 190 cc. per minute, this gives us a systemic blood flow of 3.2 liters per minute. Thus we are able to show that in this patient the pulmonary blood flow is greater than the systemic, indicating the presence of a collateral circulation from the aorta to the pulmonary artery, such as a patent ductus arteriosus.

DR. LOEB: I would just like to ask, Dr. Richards, if Dr. Humphreys made a better patent ductus with the subclavian artery than he has already, would the patient be further improved?

DR. RICHARDS: The boy is spitting up large quantities of blood.

DR. LOEB: You think that is the result of his ductus at the present time?

DR. BALDWIN: That is the result of the congestion in the lungs. Certainly by x-ray they show very dark and thick vascular shadows.

DR. LOEB: Another thing I would like to ask is whether or not you are justified in assuming that there are 26 volumes per cent of oxygen in the pulmonary vein in an individual who has as much back presssure in the lungs as this patient has had for a long time?

DR. RICHARDS: If it were less, that would make the pulmonary blood flow even larger.

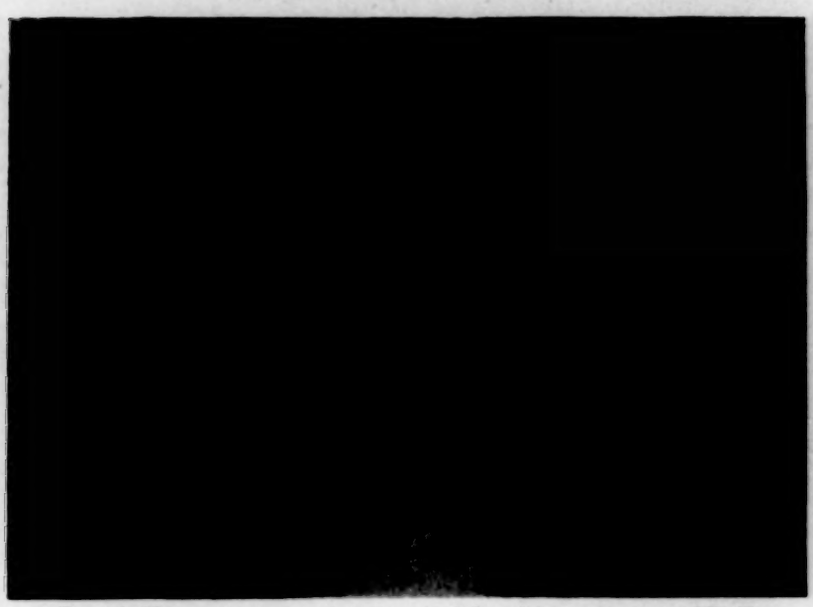


FIG. 10. X-ray showing catheter in the left pulmonary artery of D. F.

DR. BALDWIN: The smallest the pulmonary blood flow can be, assuming that the blood coming back from the pulmonary vein is 100 per cent saturated, is 3.9 liters which is still above his systemic circulation.

DR. RICHARDS: The polycythemic response is still not entirely solved, is it? In general, it corresponds with the amount of arterial oxygen unsaturation, but here is a boy with 86 per cent arterial oxygen saturation, a very marked polycythemia and presumably a very large excess blood volume; yet patient G. G., whom Dr. Humphreys operated upon to be the same as this boy now, has lost his polycythemia (at least for the time being) and is no longer cyanotic.

DOCTOR: Do you know what G. G.'s saturation is with exercise?

DR. BALDWIN: He was ill when he came in and we thought it best not to exercise him.

DR. RICHARDS: There are, of course, many different types of congenital anomalies, some of which can be successfully explored by these technics, some not. We have presented two of the most common types today, one of the non-cyanotic and one of the cyanotic group, and have not gone further into the more complicated types. Do you want to add anything, Dr. Cournand?

DR. COURNAND: In our experience with the tetrad of Fallot, which is not as wide as Dr. Bing's in Baltimore who has catheterized over 100 patients, it is not unusual to find another anomaly, often an interauricular defect. That is how Dr. Baldwin occasionally is able to get pulmonary vein blood, or through such anomalies as implantation of the right pulmonary vein in the right auricle.

I think that it is extremely important to map out all the malformations, if possible, because the problem insofar as the surgical service is concerned is certainly different if the tetrad of Fallot is complicated by still other abnormalities. In the causation of cyanosis perhaps the most important factor is the degree of over-riding or right-sided displacement of the aorta. I believe that by our methods we can detect the amount of over-riding of the aorta. It is quite striking that the tetrad of Fallot may be associated in some cases with normal or fairly normal oxygen saturation at rest; while in others there is a very marked oxygen unsaturation at rest which is directly related to the degree of over-riding.

There is another point which I would like to mention. Although the tetrad of Fallot is supposed to have atresia or marked stenosis of the pulmonary artery, it is almost the rule that catheterization of the pulmonary

artery can be carried out with success; Dr. Bing found out, after many trials, that it was possible to pass a catheter into the pulmonary artery in almost every patient. This means that there are very few patients with real atresia and most of these patients have pulmonary stenosis.

That is about all I have to say except that follow-up studies which have been carried out on patients after Blalock's operation, chiefly in Dr. Blalock's clinic, show that the pulmonary blood flow had markedly increased and that the arterial oxygen unsaturation had markedly decreased. But it takes some time for the oxygen saturation to reach its best levels; I think it takes as much as two, three or four months to reach 86, 87 or 90 per cent.

There is one more thing which is rather interesting. There is a very marked decrease in the oxygen consumption in most of the children with congenital heart disease that have been studied. In other words, they have a basal metabolism which is consistently reduced before operation. That is borne out by the appearance of the children. After the operation the oxygen consumption is very markedly increased; the basal metabolism becomes normal.

DR. ROSS GOLDEN: What is the impression as to the value of angiocardiography?

DR. RICHARDS: I am glad you brought that up. Some of the patients at Bellevue have had it and in some instances it has been of great value. They have been subjects with large dilatations of one vessel or another. It identifies them very well. Do you want to say anything further about that, Dr. Cournand?

DR. COURNAND: We really have no competent study of patients by angiocardiography.

DR. RICHARDS: We have had one patient with aneurysm of the superior vena cava due to direct communication with one of the pulmonary veins. That was shown quite well by angiocardiography as far as the superior vena cava was concerned. It did not show the cause of the aneurysmal dilatation. In a case of hemangioma of the lung the arterial-venous communication was shown by angiocardiography. In this instance catheterization methods could only show the great increase in pulmonary blood flow. I would say that the two procedures are supplementary and, if used together, can give additional information in some instances.

DOCTOR: We have done a few angiocardiographic studies and in one case a connection between the right and left ventricles was shown.

SUMMARY

DR. FREDERICK K. HEATH: Congenital heart disease includes a wide variety of anatomic defects, about one-half of which produce significant physiologic abnormalities. This half, representing about 1 per cent of all organic heart disease and about 2 per cent of that seen in children, recently has become the center of great physiologic and surgical interest. For advances in vascular surgery have made it possible to achieve dramatic and often life-saving results in this group of patients. Coincidently, investigation by means of the intravenous catheter had progressed so far that precise diagnostic and postoperative follow-up information could be obtained. This was important since it soon became obvious that clinical appraisal based only on physical findings and statistics gave neither accurate diagnosis nor quantitative information regarding cardiac function. Important, too, is the use of radiographic technics whereby the abnormality may be visualized.

The four cases presented serve to illustrate present day technics and their limitations, how data obtained by catheterization technics are interpreted, and representative results of surgical therapy. They also emphasize the frequent occurrence of multiple defects.

By means of cardiac catheterization with simultaneous measurement of the blood oxygen content and pressures in the various chambers it is possible by application of the Fick principle to calculate cardiac output, to define the systemic and pulmonary cir-

culation in terms of volume flow per unit of time, and to estimate, when present, the *direction* of shunt flow. In connection with pressure measurements it is to be remembered that an increase in pressure may result from obstruction to flow, e.g., stenosis of the pulmonary artery, in which case the rate of flow will be decreased; or on the other hand, it may simply be due to an increased rate of flow *per se*. It is clear that information both as to pressure and rate of flow are important for interpretation.

Accurate anatomic and physiologic estimations are of invaluable aid in deciding whether or not operative interference should be helpful. Thus in simple patent ductus arteriosus an excellent result is to be expected. Of twenty-six uncomplicated cases of this condition operated upon by Dr. Humphreys only one death occurred postoperatively and only one proven recurrence was noted. When the patent ductus arteriosus is complicated by other defects, the outlook depends upon the nature of these complications. In this group the operative mortality and results are decidedly less favorable.

When indicated, i.e., cyanotic heart disease, the creation of an artificial ductus, as carried out by Dr. Blalock, may relieve cyanosis but it also increases the pulmonary blood flow and the work of the heart. Whether eventual cardiac hypertrophy and failure, pulmonary congestion and polycythemia may be postoperative sequelae is not yet clear. These findings were observed in one patient thought to have a tetrad of Fallot plus a patent ductus arteriosus from birth; yet in patients receiving an artificial ductus the disappearance of polycythemia has been encountered.

Clinico-pathologic Conference

Convulsions and Hepatic Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, D. R., (B. H. History No. 141,029), a forty-four year old white married housewife, entered the Barnes Hospital on November 11, 1946, because of convulsions. Because the patient herself was never in any condition to supply information, the history had to be obtained from her husband. The family history was of interest only in that two weeks prior to admission the patient had been exposed for one week to an aunt with tuberculosis. The patient had apparently enjoyed excellent health most of her life. Twenty years before entry she had undergone an appendectomy and fifteen years before admission her uterus, Fallopian tubes, the left ovary and a "portion" of the right ovary were removed. Subsequent to the gynecologic operation she took "sheep glands" but no information was obtainable in regard to her menstrual periods.

One year before coming to the hospital the patient began to experience hot flashes and other signs of menopause. She consulted a physician who gave her injections of an unknown nature and pills identified as benzestrol (octofollin); it was thought that she took twice the prescribed dose of the latter medication. She apparently drank large amounts of water, as much as five or six glasses during the night, and voided frequently. Approximately nine months before admission she had coated the walls of her kitchen with chlorox (sodium hypochlorite). The following day she developed anorexia, nausea and vomiting and these symptoms persisted for two weeks. Because she became very nervous, a physician prescribed elixir of alurate. Three or four months before entry she used a hair bleach and again developed severe nausea and vomiting. It was reported that she smoked two packages of cigarettes daily, drank approximately 1 pint of whiskey daily and ate irregularly. Her husband stated that the patient had always bruised easily.

One day before entry the patient seemed unusually well and much less nervous than she had been previously. That evening, however, she became intoxicated and at 3 A.M. awoke with a severe headache. Three hours later she had the first of several attacks of generalized shaking movements lasting a few minutes. During each of these episodes she was described as becoming rather rigid; her legs were extended, her arms were flexed and she shook violently. Her eyes were said to have "rolled upward." Between convulsions she was unconscious and breathed "hard." Attempts on the part of her family to reach the family physician were without avail and eighteen hours after the onset of her headache the patient was brought to the Barnes Hospital.

At the time of entry physical examination revealed her temperature to be 40.4°C., pulse 136, respirations 36 and blood pressure 130/105. The patient was a well developed, obese woman who appeared to be the stated age. She was semicomatose and mumbled incoherently at times. During the course of examination she had repeated generalized clonic convulsions at fifteen-minute intervals. The skin was dry and many purpuric

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

spots were seen. The head appeared normal; no evidence of trauma was noted. The eyeballs were soft. The pupils were dilated but reacted well to light; examination of the fundi showed a few patchy white areas along the vessels but there were no hemorrhages seen and the discs appeared normal. One observer detected the odor of acetone on the patient's breath but another examiner did not agree. The neck was not stiff. Examination of the lungs revealed them to be clear to percussion and auscultation. Because of stertorous breathing, the heart sounds could not be heard well but the heart was normal in size and no murmurs were described. The liver was slightly enlarged but the spleen could not be felt and no other abdominal masses were palpable. Neurologic examination showed no signs of meningeal irritation. The extremities were held in extension; the tendon reflexes were hyperactive throughout, particularly on the left. Positive Babinski and Hoffmann signs were elicited on the left.

Laboratory findings were as follows: Blood count: red cells, 4,260,000; hemoglobin, 13.9 Gm.; white cells, 6,340; differential count: juvenile forms, 1 per cent; stab forms, 13 per cent; segmented forms, 64 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Urinalysis: (after intravenous glucose) specific gravity, 1.018; pH, 5.5; albumin, 2 plus; sugar, 3 plus; acetone, 3 plus; sediment, 3 red blood cells per high power field. Blood chemistry: sugar, 176 mg. per cent; carbon dioxide combining power, 54.5 volumes per cent; sulfadiazine, none found. Icterus index: 61. Spectroscopic examination of the plasma (on admission): oxyhemoglobin, positive; methemoglobin, questionable trace; hemoglobin, negative; porphyrin, negative; carboxyhemoglobin, negative. Spectroscopic examination of the urine (on admission): hemoglobin, negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood culture: negative. Electrocardiogram: left axis deviation and sinus tachycardia.

On admission to the hospital diabetic acidosis was suspected; no urine could be obtained, even by catheterization, and the patient was given 1,000 cc. of 5 per cent glucose in saline intravenously and 1,000 cc. of 1/6 molar lactate and 25 units of regular insulin subcutaneously. A lumbar puncture was then performed. The initial pressure was 105 mm. in water. The fluid was clear and contained fifty red cells which were not crenated and were thought to have been due to trauma incident to the procedure itself. The other studies were as follows: protein, 48 mg. per cent; sugar, 113 mg. per cent; chloride, 431 mg. per cent; colloidal gold curve, 0000000000; Wassermann test, negative. The patient was seen in consultation by a neurologist who recommended the administration of 100 cc. of 50 per cent sucrose intravenously and avertin per rectum to control the recurring convulsions.

A second specimen of urine was obtained; it was considerably darker in color than the first. The benzidine test was strongly positive but tests for urobilinogen and bilirubin were negative.

On the day following admission the patient was observed to have constant nystagmoid movements of the eyes. An ophthalmologic consultant was asked to see the patient; although examination was difficult, the discs appeared of good color and no new findings were noted in the optic fundi. It was thought that the white areas represented old choroiditis. The neurologic findings were those of decerebrate rigidity. Blood counts were within normal limits. Urinalysis revealed specific gravity of 1.050 with 4 plus albuminuria but the urine was free of sugar, acetone or porphyrin. Urobilinogen was present in a dilution of 1:50 and the benzidine test was strongly positive. The sediment revealed a few red blood cells. Repeated blood cultures were sterile. The icterus index was 100 and the prothrombin time was normal. Tenderness was elicited over the liver and faint jaundice became apparent.

Further laboratory studies were as follows: non-protein nitrogen, 28 mg. per cent; blood sugar, 56 mg. per cent; cephalin-cholesterol flocculation test, 3 plus; pro-

thrombin time, 92 per cent of normal; bleeding time, 11½ minutes; clotting time, 5½ minutes. Blood platelet count: 55,000. Bromsulfalein dye retention: 100 per cent in 30 minutes. Van den Bergh test: direct, 5.37 mg. per cent; indirect, 6.82 mg. per cent. The urine sediment showed many granular casts and bacilli; on culture, coliform organisms were reported.

On the third hospital day the patient's sensorium was much clearer and she was partially oriented; she was able to answer questions and to carry out simple commands. The physical findings were unchanged except for the presence of Trousseau's sign which was attributed to hyperventilation. The temperature fell to 38.5°C. and blood cultures continued to be sterile. Urinalysis revealed 4 plus albumin; the sediment showed numerous casts; the benzidine test was negative. The patient's urinary output gradually diminished and her non-protein nitrogen rose slightly to 33 mg. per cent. The serum protein was 4.8 Gm. per cent with 2.9 Gm. per cent albumin and 1.9 Gm. per cent globulin. The blood calcium was 7.3 mg. per cent and the blood phosphorus 3.5 mg. per cent. The icterus index had fallen to 41 units.

On the fourth hospital day examination of the lungs revealed signs suggestive of early pneumonia at the right base. The white blood count and differential remained at normal levels. Penicillin therapy was instituted. Later that night the patient became cyanotic and oxygen was given by a nasal catheter. Because of increased mucus in the tracheobronchial tree, endotracheal suction was employed. The patient had several seizures during which she held her breath. She became extremely opisthotonic and held her hands in a tetanic position. Her neck was slightly rigid. Tetany was relieved by administration of calcium gluconate intravenously, but the patient failed rapidly and died early in the morning on November 15, 1946, her fifth hospital day.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: We are at a definite disadvantage in attempting to reach a diagnosis in this case since the patient was too ill to supply her own history and the historical information obtained from her husband was not as complete as would be desired. I think we may proceed, however, by attempting first to define the anatomic lesions and second to identify their cause. Now the first event which apparently marked the onset of the final illness was a severe headache followed by convulsions. Dr. Levy, would you like to suggest a possible central nervous system lesion?

DR. IRWIN LEVY: I think it is entirely possible that no specific central nervous system lesions will be found.

DR. ALEXANDER: Do the spinal findings rule out meningeal involvement?

DR. LEVY: Yes, I think they enable us to do so. Furthermore, the fact that the spinal fluid pressure was normal seems to me to afford strong evidence that there was no real cerebral edema. In view of the finding of purpura the possibility of hemorrhagic encephalopathy must be raised. Against such a possibility, however, is the fact that the patient improved for a day or two prior to her death whereas patients with hemorrhagic encephalopathy usually have a progressively fatal course.

DR. ALEXANDER: Am I correct then in saying that if there is a central nervous system lesion, it will lie in the cerebral substance itself rather than in the meninges?

DR. LEVY: I would agree with that statement.

DR. W. BARRY WOOD, JR.: Dr. Levy, why did this patient have convulsions?

DR. LEVY: I am unable to answer your question. During her hospital stay she had definite tetany and it is conceivable that the so-called convulsive episodes were manifestations of decerebrate rigidity during tetany. Prior to the onset of these convulsions she had been intoxicated, and the possibility of alcoholic intoxication being a contributing factor must also be mentioned.

DR. ALEXANDER: Dr. Wade, do you believe that the patient had severe structural liver damage?

DR. LEO J. WADE: Certainly the 100 per cent retention of bromsulfalein at thirty

minutes indicates rather profound liver impairment and I believe that the clinical history suggests the diagnosis of cirrhosis of the liver. It is conceivable that on two occasions hepatic insult resulted from exposure to noxious agents. I am referring to the chlorox and to the hair dye. After she was in contact with each of these substances she developed symptoms which suggested intoxication.

DR. ALEXANDER: Would you consider that the patient had acute hepatitis without cirrhosis?

DR. WADE: I think it is more likely that acute hepatitis may have been superimposed on cirrhosis; I doubt that the brief exposures to the two toxic agents mentioned were sufficient to have caused the degree of liver damage indicated by the abnormal liver function tests had not the organ already been seriously compromised.

DR. ALEXANDER: Do you believe this patient had a renal lesion, Dr. Schroeder?

DR. HENRY A. SCHROEDER: No, I think that dehydration was responsible for the urinary findings and I doubt that she had significant renal disease.

DR. ALEXANDER: In view of the fact that the albuminuria varied between 2 and 4 plus, that red cells and casts were found in the sediment and remembering that the non-protein nitrogen rose, would you like to entertain the possibility that the patient had acute nephritis?

DR. SCHROEDER: The non-protein nitrogen was really not elevated to a marked degree and I would therefore be inclined to attribute the rise to prerenal azotemia.

DR. ALEXANDER: I presume you would likewise explain the albuminuria and hematuria on that same basis?

DR. SCHROEDER: Yes, I would.

DR. ALEXANDER: Dr. MacBryde, what is your view on this point?

DR. CYRIL M. MACBRYDE: I agree with Dr. Schroeder. I do not believe that there will be serious structural changes in the kidneys.

DR. WADE: Are the renal findings not compatible with a diagnosis of arteriolar nephrosclerosis? The patient had an elevated diastolic pressure and the urinary findings are consistent with that diagnosis.

DR. ALEXANDER: The ophthalmoscopic findings were not particularly significant in the opinion of the house staff nor in the opinion of the ophthalmologic consultant. However, your suggestion is quite interesting.

DR. WADE: If this patient did have arteriolar nephrosclerosis, it is conceivable that the nervous system manifestations represented hypertensive encephalopathy.

DR. WILLIAM H. OLMSTED: I should like to suggest that hematuria was just another manifestation of the underlying process which led to purpura. In view of the fact that the patient was an alcoholic who did not enjoy a satisfactory diet the abnormal bleeding may have been based on a vitamin deficiency.

DR. ALEXANDER: Would a vitamin C or K deficiency lead to such a low platelet count? You will recall that the patient had only 65,000 platelets and the normal value in this hospital is between 400,000 and 800,000. I believe the low platelet count suggests profound damage to the bone marrow itself. Dr. Futcher, would you comment on the abnormal blood chemical findings? This patient had a low total serum protein and low calcium but the albumin-globulin ratio was normal.

DR. PALMER H. FUTCHER: I cannot explain the hypocalcemia. I do not believe that the protein was low enough to have depressed the calcium to the degree reported here.

DR. ALEXANDER: Let us now consider further the problem of hepatic damage. The patient had used a hair bleach, barbiturates and large amounts of alcohol. I am told that hair bleach is usually hydrogen peroxide; at times ammonia is added. She had likewise taken large quantities of estrogenic substances and on one occasion was exposed to chlorox. Dr. Shaffer, would you comment on the toxicity of chlorox.

DR. PHILLIP A. SHAFFER: Chlorox is quite a toxic substance but the brief exposure to chlorox which this patient underwent while washing her kitchen walls does not seem to

me to merit serious consideration as a cause of her final illness.

DR. ALEXANDER: May barbiturates produce convulsions, Dr. Levy?

DR. LEVY: In cases of severe barbiturate poisoning convulsions do occur, but rarely. As a matter of fact, as you know, barbiturates are used ordinarily to control convulsions.

DR. ALEXANDER: Would you care to comment, Dr. Graham?

DR. HELEN GRAHAM: My information regarding the composition of hair bleach is essentially the same as yours, Dr. Alexander. I agree with Dr. Levy's statement on barbiturates and convulsions.

DR. ALEXANDER: May barbiturates effect the liver?

DR. GRAHAM: Since alurate is a barbiturate with long action, it is probably not destroyed by the liver. It is said, however, that damaged livers may be further injured by large doses of barbiturates. The amount of alurate taken by this patient was uncertain, as I understand it, and therefore we cannot draw specific conclusions here.

DR. ALEXANDER: Would you comment on the effect of alcohol on the kidneys, Dr. Schroeder?

DR. SCHROEDER: It is said that for each martini one drinks, one glomerulus is lost. I know of no experimental evidence, however, which indicates that alcohol damages the kidney.

DR. ALEXANDER: Let us now consider the effect of the estrogens that this patient received. Dr. Allen, would you comment on benzestrol?

DR. WILLARD M. ALLEN: Benzestrol is a synthetic compound closely related to stilbestrol; it is 2, 4-di(p-hydrophenyl)-3-ethyl hexane. The synthetic estrogens in use today are by and large non-toxic. I know of only one case report of jaundice that was due to stilbestrol. Perhaps Dr. MacBryde would comment further on this point.

DR. MACBRYDE: In the experimental animal extremely large doses of any estrogen may cause toxic effects, among which are numbered hepatic damage and damage to the bone marrow. I believe that there have been several cases in which evidence favored the fact that the natural estrogens have been responsible for some hepatic damage. I do not believe that the synthetic estrogens are any more toxic than naturally occurring estrogens. Dr. Castrodale, Dr. Helwig, Miss Bierbaum and I studied this particular problem in dogs, using comparable amounts of estradiol and stilbestrol.[1] With both types of estrogen, there were profound effects on the bone marrow with leukopenia, severe anemia, thrombocytopenia, hemorrhages, etc. We also found evidence of fatty infiltration in the liver if either estrogen was given for a long enough time.

DR. ALEXANDER: Do you believe that the toxic effect of estrogen on the bone marrow may have led to hemolysis of red cells?

DR. MACBRYDE: I know of no evidence in that regard.

DR. ALEXANDER: It seems possible that most of the alcohol and the estrogens affected the liver adversely and the changes in the blood may perhaps have been due to estrogens. Conceivably the convulsions may have been due to alcoholic intoxication. The hemoglobinuria is unexplained.

DR. FUTCHER: Is it possible that this patient had Weil's disease?

DR. WOOD: That is a very good suggestion I believe. She had fever, evidence of liver damage, rising non-protein nitrogen, urinary abnormalities and petechiae. Weil's disease is due to an organism which is called Leptospira icterohemorrhagiae and this patient was icteric and had hemorrhagic lesions.

DR. FUTCHER: In general, leukocytosis is seen in Weil's disease and this patient had no elevation of the white count which militates against that diagnosis.

DR. ALEXANDER: In summary, this patient probably had liver disease, possibly cirrhosis with superimposed hepatitis due to exposure to estrogenic substances. If she had

[1] CASTRODALE D., BIERBAUM, O., HELWIG, E. B. and MACBRYDE, C. M. Comparative studies of the effects of estradiol and stilbestrol on the blood, liver, and bone marrow. *Endocrinology*, 29: 363, 1941.

cirrhosis, it is probable that it arose as a result of long-standing alcoholism. The general consensus of opinion is that she did not have serious renal disease but that the abnormal urinary findings represented changes due to prerenal azotemia. The possibility of vitamin deficiency has been raised and Weil's disease has been suggested. It is thought that the patient probably did not have a central nervous system lesion *per se*.

Clinical Diagnosis: Cirrhosis of the liver; ?toxic hepatitis due to estrogens; ?avitaminosis C or K; ? Weil's disease.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: At the time of autopsy external examination revealed an obese white female with definite icterus of the sclerae and questionable icterus of the skin. Over the entire skin surface numerous purple to brown small pigmented areas measuring 1 to 3 mm. in diameter were seen. These were neither elevated nor ulcerated. Inspection of the viscera showed numerous petechiae in the serous membranes of the body cavities and there were also hemorrhages in the mucosa of the entire gastrointestinal tract and in the mucosa of the bladder; very small hemorrhages were seen in the meninges. On gross examination the brain showed no visible pathologic changes and multiple sections after fixation revealed no evidence of hemorrhage or encephalomalacia. The most striking anatomic change was in the liver which was enlarged, weighing 2,650 Gm. The capsule was smooth and the substance was diffuse yellow in color. The lobular markings were indistinct. There was no accentuation of the periportal fibrous tissues. After fixation the central portions of the lobules acquired a faint green stain. The pancreas was normal in size; in its substance there were a few small areas of fat necrosis. The kidneys appeared normal. The lungs were heavy, weighing 890 Gm. There was total atelectasis of the right lower lobe and partial atelectasis involving the lower portions of both upper lobes. There were no gross changes which could be interpreted as consolidation. The spleen was slightly enlarged and weighed 180 Gm.

DR. ROBERT A. MOORE: As Dr. Johnson has told you, the gross anatomic changes in general were not very striking. There was a fatty liver, a few foci of fat necrosis about the pancreas and petechiae and ecchymoses in various parts of the body. Before discussing the diagnostic possibilities further let us examine the microscopic sections. Figure 1 is a section of the liver showing the character of the pathologic change. There is a moderate to severe degree of fatty infiltration in the liver. The liver cells are distended by large vacuoles containing fat but there is no significant increase in the amount of connective tissue. The pathologic picture is not that of so-called fatty cirrhosis but represents rather fat infiltration or fatty metamorphosis. That the liver cells were still capable of some function is evidenced by the fact that a glycogen stain revealed the presence of glycogen in the cytoplasm of many cells. Conceivably the glycogen was deposited after the intravenous infusion of glucose. Figure 2 is from the pancreas. It shows an area of fat necrosis. The fat cells are no longer distinctly visible for the fat has been converted into granular, amorphous material without giving rise to much cellular reaction. The pancreatic lesions occurred toward the end of the patient's life and probably do not represent any change of clinical significance although they may aid us in arriving at our final evaluation. Figure 3 is from the heart and shows two types of change from the normal: First, there is interstitial edema which is evidenced by the separation of the muscle fibers and secondly, there is slight cellular infiltration. In Figure 4 another section of the heart muscle is seen showing the same changes just outlined plus some degenerative changes in the fibers. In Figure 5 these changes are seen under higher magnification. Most of the cellular infiltration is due to an increase in the myocytes of Anitschkow, a change which arises as a result of irritation in the myocardium. It is generally believed that

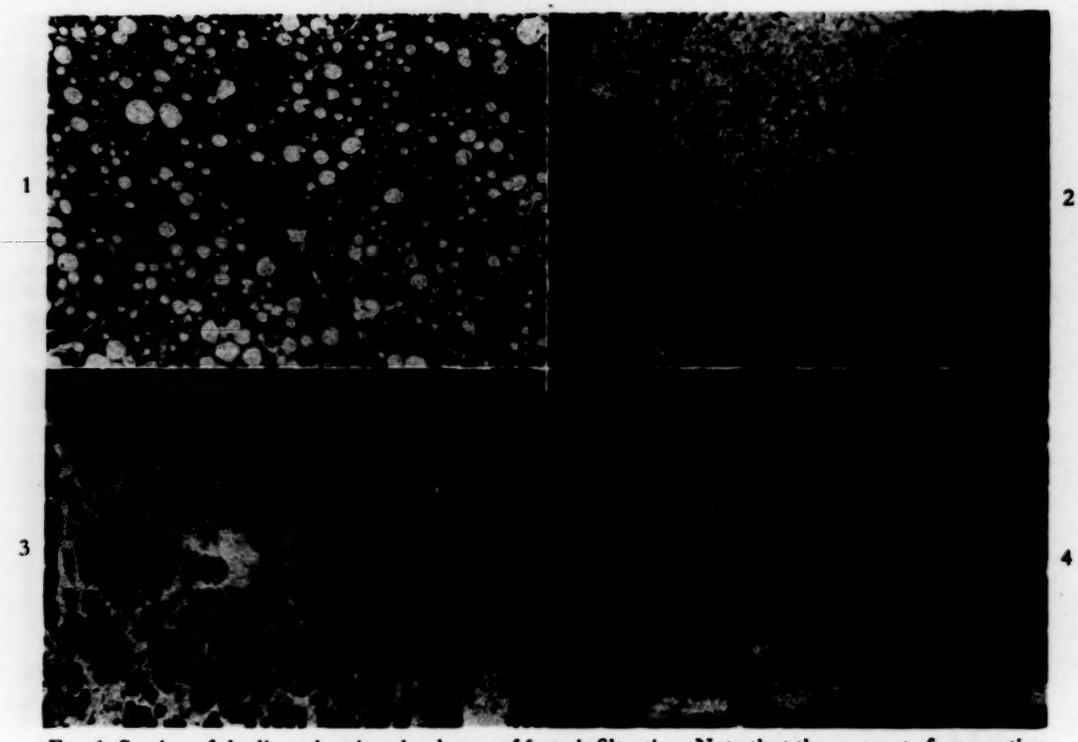


FIG. 1. Section of the liver showing the degree of fatty infiltration. Note that the amount of connective tissue is not increased over that seen normally.
FIG. 2. Section of the pancreas in an area of fat necrosis.
FIG. 3. Section of the myocardium showing interstitial edema and slight cellular infiltration.
FIG. 4. Another section of the myocardium showing the same changes seen in Figure 3.

the Anitschkow myocytes develop into Aschoff cells. In other words, almost any noxious stimulus may bring about activation of the myocyte of Anitschkow while in acute rheumatic fever the causative agent, whatever it may be, causes further change in the cells to the point when they take on the characteristics which we ascribe to Aschoff cells. In Figure 6 a section of skeletal muscle is seen. We examined a number of sections of the skeletal muscle and all showed the same change. The lesions were most advanced in the diaphragm and consisted of degeneration of the muscle fibers, proliferation or accumulation of sarcolemmal cells and slight infiltration of mononuclear cells. In other words, there is degeneration and slight inflammatory reaction in the striated muscles, both skeletal and cardiac. Figure 7 shows a section of the adrenal gland; one sees a zonal type of necrosis in the center of the cortex. Finally a section of the lung (Fig. 8) shows the changes of terminal bronchopneumonia. The bronchi are filled with an exudate consisting of polymorphonuclear leukocytes and in some areas the alveoli are filled with a similar exudate.

In attempting to correlate the changes it will be well to list the pathologic changes which may be related to the primary disease: First, there is moderately advanced fatty metamorphosis of the liver; second, degenerative changes with some proliferation which involve the heart muscle and the skeletal muscle; third, in the pancreas there is focal fat necrosis; fourth, the bone marrow is generally hypoplastic, all the elements apparently being equally depressed and fifth, in the adrenal, areas of cortical degeneration were present. The negative observations may be of significance. There were no changes either grossly or microscopically in the central nervous system and the kidneys were normal grossly and microscopically.

Certainly the changes in the liver may be

FIG. 5. Section of the myocardium seen with higher magnification. Note the increase in the Anitschkow myocytes.
FIG. 6. A section of skeletal muscle showing degenerative and proliferative changes.
FIG. 7. Section of the adrenal cortex showing the zonal type of necrosis.
FIG. 8. Section of the lung through an area of bronchopneumonia.

attributed to the chronic alcoholism for the lesion is well recognized pathologically.[2,3] It has been recorded several times in patients who developed fatty metamorphosis of the liver in association with chronic alcoholism and who came into the hospital with convulsions; some of these patients have died soon after admission and at autopsy the only significant pathologic change has been the fatty metamorphosis in the liver. Likewise pancreatic changes, such as those described herein, have been observed not infrequently in chronic alcoholics. Changes in the striated muscle are similar to those which have been described by Follis[4] as vitamin B deficiency or they may be produced by combining thiamine and potassium deficiency.

[2] LE COUNT, E. R. and SINGER, H. A. Fat replacement of the glycogen in the liver as a cause of death. *Arch. Path.*, 1: 84, 1926.

[3] GRAHAM, R. L. Sudden death in young adults in association with fatty liver. *Bull. Johns Hopkins Hosp.*, 74: 16, 1944.

[4] FOLLIS, R. H., JR. Myocardial necroses in rats on a low-potassium diet prevented by thiamine deficiency. *Bull. Johns Hopkins Hosp.*, 71: 235, 1942.

May the changes in the bone marrow and in the adrenal have resulted from the long continued use of estrogenic substance? The bone marrow changes particularly may possibly have been due to the estrogens for the changes were those of general hypoplasia rather than of inanition.

The clinical correlation in this case is not too satisfactory. The encephalopathic symptoms may have been due to hepatic damage or possibly to thiamine deficiency. We are unable to explain the tetany and the cause of the petechial hemorrhages is still obscure. I assume from the clinical discussion that hypoprothrombinemia was excluded on the basis of the normal prothrombin time. The changes in the megakaryocytes in the bone marrow were not impressive, certainly not to the point at which one would be willing to attribute the hemorrhage to thrombocytopenia. That the hemorrhage could have been due to low fibrinogen seems unlikely. Although the blood proteins were lower than normal, it does not seem likely

that they were low enough to allow the fibrinogen to become significantly depressed. It is the last element whose level falls and it is the rarest cause of hemorrhage. Vitamin C deficiency must certainly be considered. I do not think that either the hair bleach or chlorox should be considered as possible causative agents because of the remote exposure, but I do acknowledge Dr. Wade's point, namely, that a very fatty liver may have been much more susceptible than a normal one, even to brief exposures to these toxic agents. I do not think the changes are related to barbiturate. I believe we can rule out Weil's disease since the pathologic changes are not consistent with the diagnosis and in suitably stained sections no organisms could be demonstrated.

In summary we are left with the possibility that either alcoholism or estrogen toxicity were causative agents and I do not know how one could distinguish between them. Certainly the entire clinical picture with the exception of bone marrow changes may be explained on the basis of chronic alcoholism and the bone marrow changes may have resulted from large amounts of estrogens. Personally I believe the alcoholism was more significant than was the estrogen therapy. It is of interest that patients dying of fatty metamorphosis of the liver do so during the winter. The syndrome is not seen in the summer.

DR. WOOD: Were the myocardial changes those of beri-beri?

DR. MOORE: Conceivably.

DR. WADE: Do you believe that the liver changes would have gone on to cirrhosis?

DR. MOORE: Yes, I do. Long-continued fat infiltration in the liver will result in fibrous proliferation.

Final Anatomic Diagnosis: Fatty metamorphosis of the liver, advanced (history of chronic alcoholism); petechiae in skin, serous membranes, mucus of stomach, small and large intestines, endocardium, mucosa of trachea and bronchi; focal hemorrhages in mucosa of bladder and in subarachnoid space, slight; atelectasis of entire lower lobe of right lung and dependent portions of all lobes; bronchopneumonia; fat necrosis in body and tail of pancreas; focal necroses in the cortex of the adrenal glands; degeneration of skeletal muscle with proliferation of sarcolemma; focal degeneration of myocardium with proliferation of myocytes, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Gout in a Negro Family*

ABRAHAM COHEN, M.D.

Philadelphia, Pennsylvania

THERE is little if anything in medical literature on the incidence of gout among the Negro people. This report concerns two of three Negro brothers who have gout. They exhibit the classic manifestations of tophaceous gout, as indicated in Figures 1 to 9.

It has always been thought that gout was a disease of the gourmand and the wealthy. The mode of life of these patients would hardly be considered that of gourmands and they were certainly not of the wealthy class.

Gout has been reported in these Negro patients on another occasion.[1] However, since the last report another brother has developed the disease. Opportunity is taken here to report on the progress of the disease in these patients.

CASE REPORTS

CASE I. J. A., a Negro male, born in South Carolina in 1914, 5 feet 9 inches tall, weighed 128 pounds. He had the ordinary diseases of childhood. The family history was irrelevant except that a younger brother has gout.

The onset of the present illness dates back to when he was twelve years of age. At this age he would awaken during the night with stiffness and swelling in the right knee. This lasted for a week, was not accompanied by pain and did not confine him to bed. He made a complete recovery. A year later he was awakened one night by severe pain in the right knee and found that the joint was swollen. The pain and swelling lasted for ten days, were confined to the knee and did not keep the patient in bed. He again made a complete recovery. At this time the patient was residing in the country in South Carolina. The family was poor and could afford only an ordinary diet. The patient ate sparingly of proteins and was not a drinker of alcohol.

About two years later, while at work one morning, he noticed swelling in the right great toe and left ankle. Soon there was redness, heat and severe pain. A few days later the right knee became involved and the patient was forced to bed for the first time. Here he remained, unattended by a physician for two weeks. A good recovery was made without residual signs or symptoms and no further difficulty was experienced until six years later, at the age of twenty-two, when at work pain and swelling developed suddenly in the right metacarpophalangeal joint. This attack was very painful and lasted for one week. The following week the right elbow became similarly involved. This was followed by involvement of the left great toe, right ankle and right knee. All joints were red, hot, swollen and extremely painful. Three weeks were spent in the hospital where treatment was given for arthritis.

FIG. 1. Gout involving all toes in Negro.

There were ten more visits to the hospital. Fever therapy, baking and massage, as well as the other forms of therapy ordinarily prescribed for arthritis were given trial. The longest stay in the hospital was nineteen days, the shortest seven days.

* From the Arthritis Clinic of the Philadelphia General Hospital.

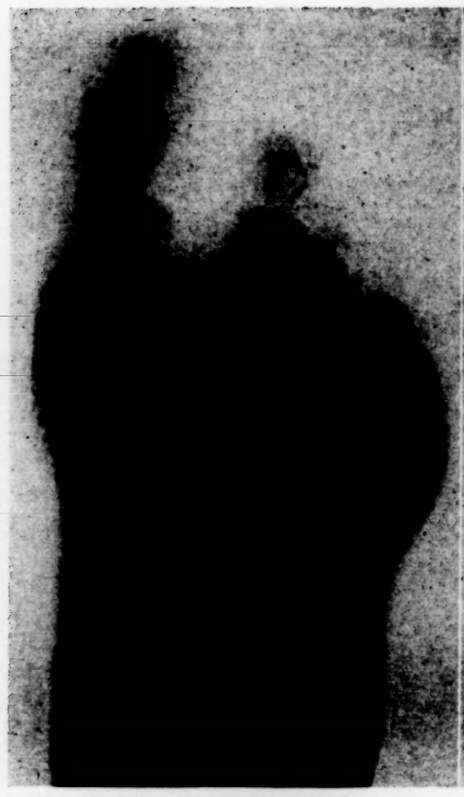


FIG. 2. X-ray of right foot in Figure 1.

FIG. 3. X-ray of left foot in Figure 1.

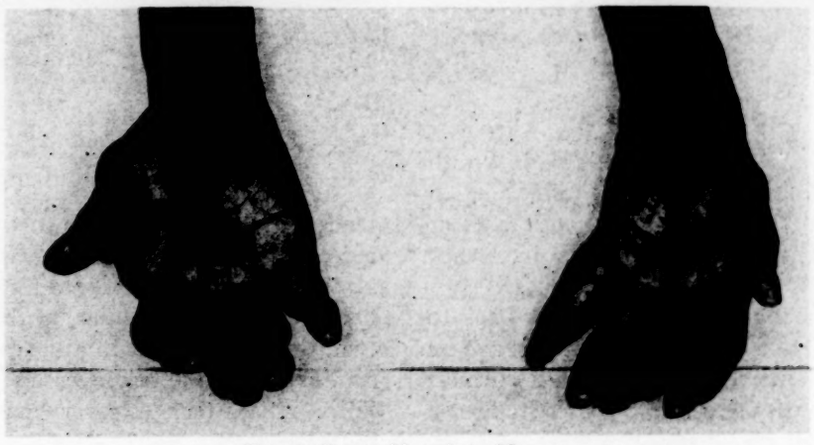


FIG. 4. Gout of hands in Negro.

The ears showed tophi. (Fig. 9.) Heart, lungs and abdomen were normal. The extremities showed large tophi involving both olecranon bursae, wrists, fingers, knees and toes. It was necessary to amputate one toe since its increase in size made it extremely difficult for the patient to walk. The blood uric acid varied from 11 to 5 mg. per cent.

His diet consists of whatever he can get and he takes colchicin whenever he can get it. Due to the shortage of colchicin during the war period and even at the present time, he seldom takes it unless we can find it for him. In the interim we have watched him go from bad to worse until on one occasion we found it necessary to amputate a toe so that walking could be facilitated.

Of all the cases of gout seen by the author this has been the most fulminating.

CASE II. P. A., a Negro male, born in South Carolina in 1924, had the ordinary diseases of childhood. One brother has tophaceous gout. At the age of twelve, during the night, he was suddenly awakened with severe pain in the left

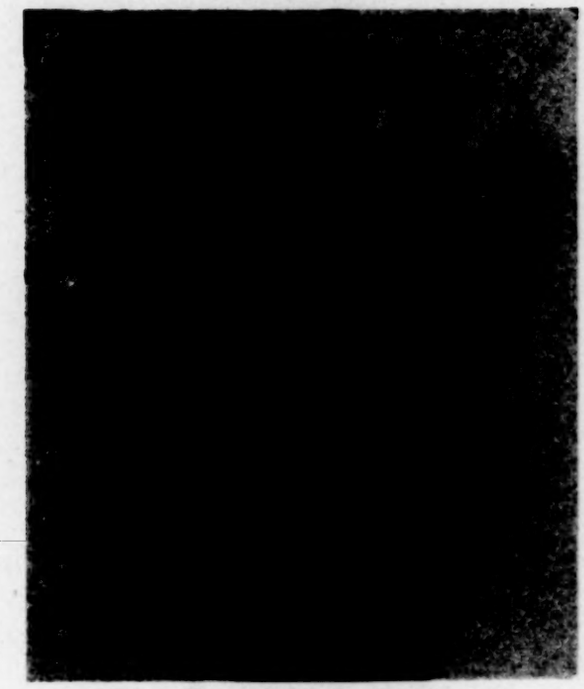


FIG. 5. X-ray of right hand in Figure 4.

FIG. 6. Gout of hands in Negro.

heel. In the morning there was swelling accompanied by pain along Achilles tendon. The attack was confined to the heel and lasted about two weeks. He made a good recovery without residual signs or symptoms.

Two years later, at the age of fourteen, he was again awakened in the night with pain, swelling and extreme tenderness in the left great toe. This time the attack lasted a week. No other joints were involved.

The third attack came at the age of sixteen; the right great toe and left ankle were involved. The patient was confined to bed for ten days. There was swelling, redness and severe pain particularly at night. At the end of ten days recovery was complete except for the residual swelling. He has averaged two attacks yearly ever since.

Examination reveals a negro boy, twenty-two years of age, weighing 118 pounds, 5 feet, 3 inches in height. His blood uric acid (serum) is 6.1 mg. per cent. X-ray examination of the left great toe shows a punched-out area at the left first metatarsophalangeal joint.

Since the age of twelve this patient gets about four attacks yearly. He has tophaceous gout.

FIG. 7. X-ray of left hand in Figure 4.

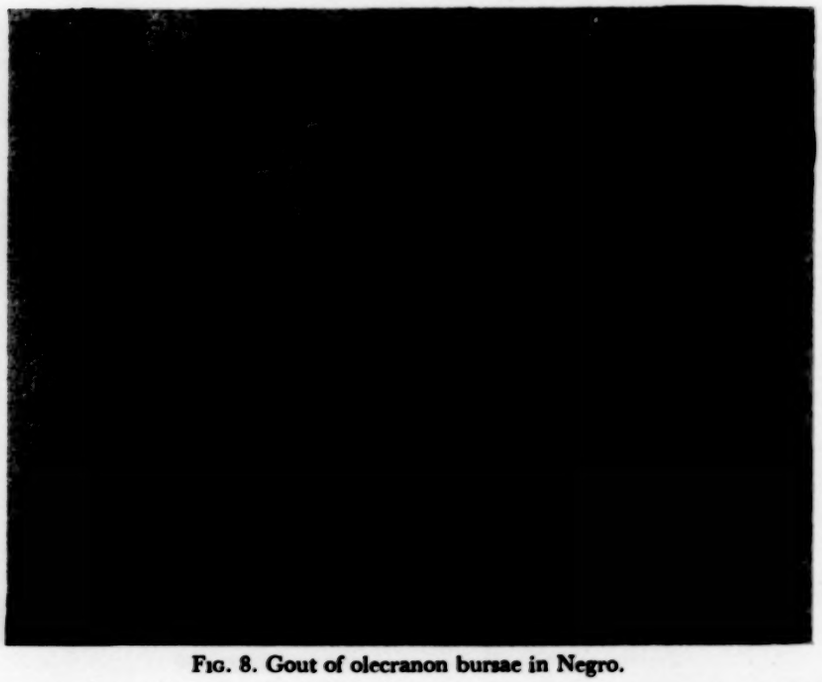


FIG. 8. Gout of olecranon bursae in Negro.

The blood uric acid ranges from 7 to 5.5 mg. per cent.

During the last two years another brother, older than J. A., has developed pains in his joints described by J. A. as typical attacks such as he himself has. There are tophi in the ear cartilages. He refuses to visit the hospital nor does he wish to be seen by a physician.

Table 1 represents the genealogy for three generations as obtained from the family bible.

In 1938 the author[2] suggested a method for prevention of attacks of gout. It is of interest to note that our patients with presumptive gout who adhere to the regimen as described consider themselves to all in-

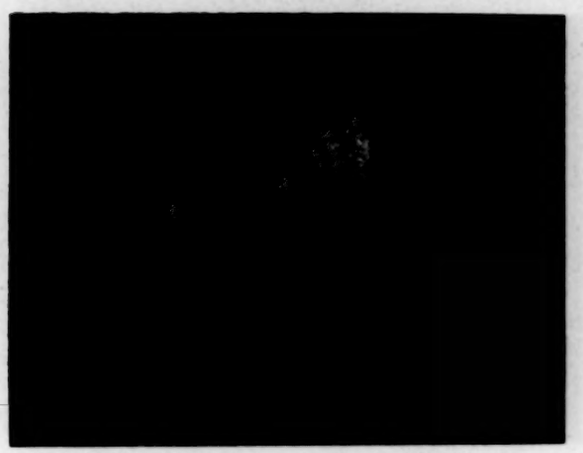
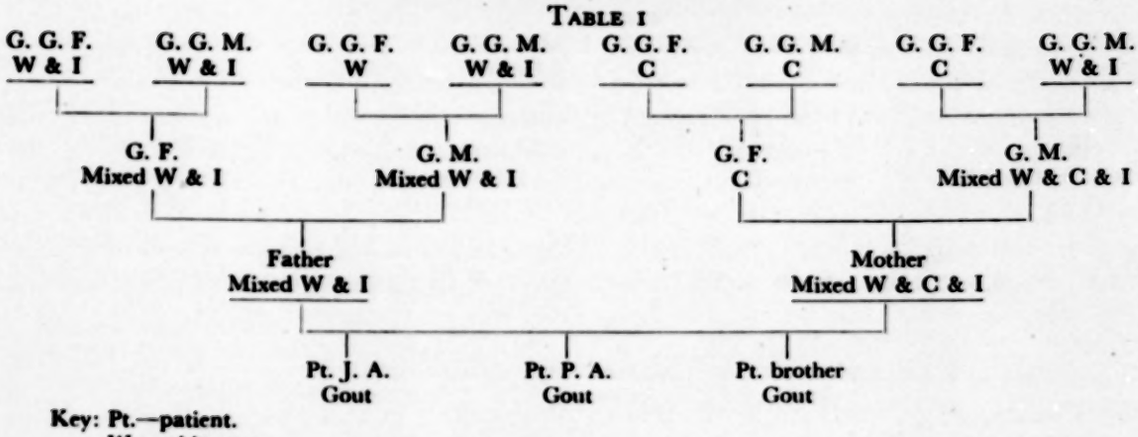


FIG. 9.—Tophus in ear cartilage of Negro.

TABLE I


G. G. F. W & I
G. G. M. W & I
G. G. F. W
G. G. M. W & I
G. G. F. C
G. G. M. C
G. G. F. C
G. G. M. W & I
G. F. Mixed W & I
G. M. Mixed W & I
G. F. C
G. M. Mixed W & C & I
Father Mixed W & I
Mother Mixed W & C & I
Pt. J. A. Gout
Pt. P. A. Gout
Pt. brother Gout

Key: Pt.—patient.
W.—white race.
I.—indian race.
C.—colored race.

tents and purposes "cured." With proper regulation of the diet, abstinence from alcoholic beverages, proper administration of colchicin (and barring surgery, infection and accidents), one need never have a recurrent attack of acute gout. On the other hand while our tophaceous cases rarely get attacks, the progress of this disease goes on unabated. Such has been the experience of the patient in Case 1 and of all those with tophaceous gout under our care.

REFERENCES

1. COHEN, A. Gout and the Negro. *South. Med. & Surg.*, 103: 654–655, 1941.
2. COHEN, A. Gout among arthritics. *Pennsylvania M. J.*, 41: 1100–1104, 1938.

Long-standing Case of Widespread Tuberculosis and Acute Colon Bacillus Infection Treated by Streptomycin

WM. EGBERT ROBERTSON, M.D.
Philadelphia, Pennsylvania

ALTHOUGH the Actinomyces group has been studied by Waksman since 1919,[1] the production of streptomycin from Actinomyces griseus, the most recent to be studied, has until recently been very limited. In April, 1944, a small amount was placed in the hands of Doctors Hinshaw and Feldman of the Mayo group by Dr. S. A. Waksman. These investigators stated that "This amount was adequate to treat only four tuberculous guinea pigs for a limited period, but the results were sufficiently impressive to cause us to visit Dr. Waksman's laboratory immediately, in order to discuss these findings and to plan for future studies on an adequate scale. The amount of material required for such experiments was beyond the productive capacity of Dr. Waksman's experimental laboratory, but with his help it was possible to enlist the aid of Merck & Company who soon supplied streptomycin for earlier experimental problems.[2] Thus it has become possible for the Mayo group to treat "more than one hundred patients who had various infectious diseases" and to initiate a valuable and highly encouraging experimental study of tuberculous guinea pigs. This latter study by Feldman, Hinshaw and Mann[3] furnishes a greater degree of encouragment than does the clinical study of streptomycin in human tuberculosis by Hinshaw and Feldman.[4] In the experimental work forty-nine guinea pigs were used, twenty-four untreated controls and twenty-five treated by 1,500 units of streptomycin given subcutaneously every six hours, beginning on the forty-ninth day after inoculation with a human strain of Mycobacterium tuberculosis and continuing for 166 days. Seventy per cent of the controls died before the study was completed and all but two of the treated guinea pigs survived. Most remarkable was the fact that thirteen of the treated animals recovered and no trace of the infection was found except for a calcified tubercle in the lung of one animal. In eleven of the remainder microscopic tubercles were found in the spleen, all retrogressing, seven of them being calcified, three fibrotic and one an epithelioid lesion.

Much less favorable is the impression gained by the study of thirty-four cases of tuberculosis in humans by Hinshaw, Feldman and colleagues previously referred to. They insist upon the time factor as a very necessary condition in judging the results, also the importance of not neglecting the use of rest, pneumothorax and any other measures previously found of value in the management of human tuberculosis. In the sixteen pulmonary cases the results were not spectacular, but streptomycin was limited in amount and dosage was not definitely established at that time. Clinical improvement did not run parallel with roentgenographic improvement but in two patients with miliary tuberculosis, one of whom had renal tuberculosis, improvement was "unmistakable and striking." This latter patient and four others with genitourinary tuberculosis, all having but one kidney, gave more satisfactory results. In four of these patients the Mycobacterium tuberculosis disappeared from the urine in two to four weeks, remained absent during the period

of one to four months during which they were under observation and the organism was not recovered, either by culture or by guinea pig inoculation. In the fifth patient, the one with miliary tuberculosis, although roentgenologic examination of the lungs showed definite improvement, the organism persisted in the urine. Four subjects with tuberculous empyema treated by streptomycin introduced into the pleura were not benefited and the medicament proved irritating. Six patients had tuberculous skin lesions, three with "draining sinuses due to suppurative tuberculous lymphadenitis." These showed "prompt and striking response" to streptomycin. Too brief a period had elapsed to pass a final opinion; this was also true of a case of tuberculous laryngitis.

The authors point out that a larger series treated over a sufficiently long time and with sufficient dosage, which remains to be determined, may not sustain the relatively favorable impression which may be deduced from their report. They urge strongly against optimism at this time, just as did Dr. Hobart Reimann and co-authors[5] in their five cases of typhoid fever treated by streptomycin. The author has recently seen a patient with typhoid fever who was given two million units daily intramuscularly and one million units by mouth. This patient died of hemorrhage of the bowel and perforation in the third week of the disease after five days of streptomycin.

In both of the granulomatous diseases, syphilis and tubercuolsis, some years must elapse before final judgment can be passed as to the therapeutic value of penicillin in syphilis and streptomycin in tuberculosis although reports thus far published suggest at least a measure of encouragement, even more striking in syphilis treated with penicillin.

Much remains to be learned as to the efficacy of streptomycin, but its value has been definitely established in meningitis due to H. Influenzae, Friedländer bacillus infection (which also responds well to some of the sulphones given by vein), tularemia and in infections due to gram-negative organisms involving the genitourinary tract and peritoneum. Thus far, it is of questionable value in undulant fever and typhoid fever. In this latter streptomycin is given also by mouth because it diffuses only slightly out of the bowel, most of it being recoverable in the stool[6] and it causes fairly prompt disappearance of the typhoid bacilli from the stool, but they return if, for any reason streptomycin is stopped in the course of the disease. In pulmonary tuberculosis with tubercle bacilli present in the sputum, even though clinical improvement occurs, the organism has not disappeared from the sputum in the cases reported thus far. If streptomycin were really bactericidal *in vivo*, this would not be the case in such infections. In treating more chronic infections, if for any reason the administration of streptomycin is stopped, to be resumed at a later period, definite sensitization phenomena may occur, mentioned also by Hinshaw and Feldman.

In the case of widely disseminated tuberculosis the patient developed manifestations of a histamine-like reaction and hematuria soon after the remedy was originally injected, with chilliness, marked depression, lowering of blood pressure, anorexia, general muscular soreness and a rapid pulse. The hematuria did not cease until a weak silver nitrate solution was instilled into the bladder. Streptomycin was temporarily stopped and when it was resumed he developed a fever up to 100°F., depression, a marked drop in blood pressure to less than 90 systolic, a pulse rate of 120 to 130, chilliness and hematuria, although the unit dose was much smaller than in the initial period. In the beginning too, he developed vestibular phenomena but no deafness. In both instances hydrochloride was used, so that the manifestations were probably due to the remedy itself and not to any impurities.

Streptomycin has been given directly into the vein and into the pleura and subdural space.[7] Most frequent and satisfactory is its administration by the subcutaneous or intramuscular route. It is only slightly irritating locally but of short duration, diffuses

rapidly and can be recovered from blood, urine, bile, ascitic fluid, pleural fluid, amniotic fluid, peritoneal cavity, aqueous and vitreous humors and small amounts in spinal fluid. The dose, avenue of administration and time are all factors in determining the rate of absorption and excretion. It is very soluble, one million units (1 Gm.) being taken up readily by 5 cc. or less of distilled water or physiologic salt solution, but the amount of diluent depends on the dose to be given every three or four hours during the twenty-four hours. It has also been administered by nebulization and has not been found to be irritating but recovery is then negligible in blood and urine.

Reactions undoubtedly occur, proportionate to the dose, and are even more marked with smaller doses when the drug is re-administered after a lapse in treatment. Now that streptomycin has been crystallized and hydrochloride produced, it would seem to indicate that the reaction is inherent and not due to impurities. Pyrogens in the diluting fluid must be considered but careful technic will minimize or prevent these. Then too, these are more apt to occur when intravenous injections are given, but marked systemic disturbances and mild febrile reactions are not infrequent with streptomycin when subcutaneous or intramuscular routes are employed.

CASE REPORT

A male, age forty-one, a practicing physician, was seen first in 1927 when a sophomore medical student. He had had minimal pulmonary tuberculosis and bilateral pleurisy, 35 ounces of clear serum being removed from left pleura, dry tap on right. He had been given a hypodermic of quinine and urea in the right arm and when the author first saw him he had partial paralysis with wrist drop and atrophy. Immediate operation was advised which was done by Dr. Wayne Babcock with good recovery and a useful hand. Underweight, but without definite evidence of pulmonary involvement, in 1928 he spent two months at Trudeau Sanitarium. Soon thereafter he developed an epididymitis on the right side, was operated upon by Dr. George Mueller with a diathermy knife and began to improve in health and weight. Some time later he developed involvement of the left epididymis, but this opened spontaneously and soon healed. He lost a year at medical school but later concluded his course and internship. In 1928, rectal examination revealed some involvement of prostate and seminal vesicles, the right one especially, and later an involvement of the right testicle which became moderately enlarged and a hydrocele developed. He then consulted Dr. Hugh Young in Baltimore who advised widespread removal of the affected organs, without which Dr. Young said the patient would not live ten years. Operation was not accepted but he continued to gain, adding about 30 pounds in a few years, appearing well and leading an active life, his weight exceeding any previous period. This state of well being continued until tubercle bacilli were found in his urine and even for some time thereafter. Then began a series of cystoscopies and intravenous pyelograms at the hands of Dr. Lorenzo Milliken who removed a tuberculous kindey in April, 1943. A loss of 10 pounds followed; this was only partly regained but he resumed his activities. Tubercle bacilli did not disappear from the urine however.

Early in 1944 he developed a deep urethral obstruction, believed by Dr. Milliken to have been due to a tuberculous lesion. Again he was hospitalized and the stricture dilated. This had to be followed for a time by instrumentation and at times by catheterization. Slight hematuria persisted. Quite possibly the instrumentation was the source of a colon infection and of a severe illness which again required hospital care. He was admitted on September 25, 1945. Chill, temperature rise to 104°F. and colon bacilli were found in blood stream and urine and numbers of Mycobacterium tuberculosis also in urine, singly and in clusters. The colon infection suggested the use of streptomycin and this was obtained on October 8, 1945, through Dr. J. M. Carlisle of Merck & Company who suggested that we begin with three million units every twenty-four hours. Meanwhile his urine was kept at a pH of 5 to 5.5 and he was given glucose and saline and whole blood transfusions. Fever subsided gradually, reaching normal in a week but on October 6, 1945, eleven days after admission, he had a chill, temperature rose from 98°F. to 103.4°F. and to 104.4°F. the next two days, typical spiked elevations. His urine became very thick and had the appearance and consistency of dirty cream, due to pus with

some blood. Blood cultures became negative for colon organisms in forty-eight hours but they persisted in the urine until streptomycin had been given for five days. Urine culture was positive for colon organisms on October 5th, streptomycin was begun on October 8th and the next urine culture on October 13th was negative and remained negative. Acid-fast bacilli disappeared on October 17th, nine days after streptomycin was begun, remained absent on smears, culture and by guinea pig inoculation for a period of eight months when they reappeared. At this time we were able to procure 8 Gm. of the antibiotic and again the acid-fast bacilli began to disappear to the extent that they were difficult to find. He had received streptomycin originally from October 8th to November 19, 1945, this being continued after his return home on November, 2 1945, until a total of 35 million units (35 Gm. of the hydrochloride) had been given, 3 million units daily for three days, 2 million for one day, then 1½ million for one day, followed by one million units October 27, 1945. Three days elapsed before a new supply was received. This was given in daily doses of ½ million units, in part because of the difficulty in obtaining the drug and in part because of his reaction. He had been seriously ill but because of the severe headache, prostration, chilliness and vertigo which attended the large doses, it seemed expedient to reduce the daily amount. The urine cleared rapidly, pus disappeared, but traces of blood persisted, the volume increased and temperature became normal five days after the streptomycin was first given, at four-hour intervals subcutaneously. There was no consistent drop in blood pressure which could be ascribed to the drug. The CO_2 combining power was 49 mgs. per cent and blood urea nitrogen 16 mg. per cent on admission. This rose gradually to 42 vols. per cent on October 29, 1945 but fell gradually to normal and has since remained normal. Red cell counts and hemoglobin were good at all times, practically normal, but leukocytes remained high throughout, from 23,600 on admission to 39,800 on October 7, 1945, to fall slowly after the streptomycin was started on October 8th but not to normal. Many young forms were usually present and a definite left shift. Reticulocyte counts ranged from 0.3 per cent to 0.5 per cent. We have noted an elevation of blood urea in another patient receiving streptomycin but cannot say unequivocally that this is due to the drug. If it were, the effect is not likely to be parenchymatous, judging from cases of uncomplicated nephrosis where blood urea levels are relatively normal. One would expect it to be due to vascular and perivascular irritation thus involving the glomeruli.[9]

Specimens collected October 25, 1945, when the patient was receiving one million units every twenty-four hours were as follows: Serum concentration 15.1 units per cc., approximately 7.5 units per cc. of whole blood, urine concentration 256 units per cc. Determinations also were made separately on these specimens by an experienced person. The figures reveal a striking similarity. Serum concentration 16 units per cc., representing 8 units per cc. of whole blood; urine concentration 60 units per cc. The organism used in all of the studies was the staphylococcus, S. M. strain furnished us through the courtesy of Merck & Company. A specimen of this urine, centrifuged at high speed, contained innumerable red blood cells and many leukocytes but was negative for organisms, including acid-fast bacilli.

A second series of specimens collected November 9, 1945, the dosage of streptomycin now being 500,000 units per twenty-four hours, revealed: Serum concentration of 10.6 units per cc., or approximately 5.5 units per cc. of whole blood; urine concentration 245 units per cc.; urine output about 2200 cc. in twenty four hours. Duplicate studies in another laboratory as previously noted, using the same S.M. strain staphylococcus, showed serum concentration of 14.6 units per cc.; urine concentration 271 units per cc. There were only a few red cells and an occasional white cell present in the urine, but no acid-fast bacilli.

A third study made when only 500,000 units were being given every forty-eight hours disclosed a serum concentration of 8.6 units per cc., or approximately 4.3 units per cc. of whole blood; urine concentration 96.4 units per cc.; negative for tubercle bacilli and relatively few red blood cells in the sediment of a 100 cc. centrifuged specimen.

The patient convalesced slowly, His heart rate varied from 100 to 120 on slight effort which was not explained upon physical examination. He gradually resumed his professional duties under limited conditions. Early in the following March of 1946 he had a temporary upset, slight sore throat, headache, malaise and a little temperature rise with pulse still rapid.

The patient elected to take penicillin orally, 250,000 units per day. The blood level was determined nearly twenty-four hours after the last dose, hence it was less than one unit per cc. of serum. The urine volume was 1950 cc. in twenty-four hours, 2 units per cc. or 3900 units in twenty-four hours. Blood was present microscopically but no acid-fast bacilli were found. Blood urea nitrogen was 12 mg. per cent. After four weeks of incubation culture was negative for acid-fast organisms. Early in April, 1946, blood count showed a slight microcytic anemia with 7100 leukocytes, normal differential. Blood urea nitrogen was again 12 mg. per cent and creatinin 1.5 mg. per cent. Early in July, 1946, tubercle bacilli were again found in the urine; also many pus cells and erythrocytes and, on culture of urine, staphylococcus albus, nonhemolytic streptococci and diphtheroids. Fortunately a small amount of streptomycin was obtained and he was given one million units daily for four days. After receiving 2,125,000 units by subcutaneous injection, the serum level was 9½ units, the urine level 252 units per cc., an approximate recovery of 56 per cent in the urine. Many acid-fast bacilli were found. He reacted promptly to the drug, not having had any for eight months. He received one million units daily by subcutaneous injection for four days but his malaise became profound, he again developed headache and vertigo, although he did not complain of deafness and he developed a fever of a little over 100°F. Incapacitated for work, he begged for smaller doses. Streptomycin was reduced to 250,000 units every twenty-four hours, given at six-hour intervals, largely because the total supply of streptomycin was limited. This episode was rather more suggestive of a sensitizing reaction than of any toxic property in the drug itself. His blood pressure, usually 100 to 110 systolic, fell to 90 systolic and 60 diastolic during the attack. Another determination of the levels was made between the second and third days of a dosage of one million units per day intramuscularly: Serum level 9.5 units; urine level 252 units, a recovery of about 56 per cent. Acid-fast bacilli were present and not difficult to find.

Neither the time factor nor the dose had thus far made any definite impress. In the initial period of streptomycin dosage, eight months prior, the three days of three million units per day, followed by a gradual reduction may have avoided any possibility of drug fastness. It is certain that the total disappearance of the organism, the gain in weight and return to physical efficiency in this patient gave evidence of at least bacteriostatic action of the drug and encourage the hope that an available supply and sufficient dosage of streptomycin may arrest an incipient case of tuberculosis and restore efficiency for gainful occupation in one even with such diverse and widespread manifestations as presented by this patient. Of course, the long period of infection may have resulted in some degree of immunization.

COMMENTS

Dr. Waksman[10] has been working with the Actinomyces group of soil organisms since 1919, but it was not until 1940 that he produced streptothricin obtained from Streptomyces lavendulae,[11] the first antibiotic capable of acting against both gram-positive and gram-negative organisms. In 1944,[12] streptomycin was produced from Streptomyces griseus. This has proved to be relatively non-toxic in the doses thus far employed. A histamine-like[13] reaction may occur, especially when, for any reason, the drug has been stopped, to be used again after a lapse of some weeks. The drug has been proved active against a wide range of pathogenic organisms, both gram-positive and gram-negative.[14] This has been true both *in vitro* and in experimental animals and against certain infections in humans. No two lots of streptomycin assay alike. The unit strength varies. These units of antibiotic substances express their antibacterial properties as measured against some test organism, ascertaining the smallest quantity of the drug necessary to inhibit the growth of staphylococci, E. coli, B. subtilis and a hemolytic organism such as B. megatherium,[15] in 1 cc. of broth, using the slide cell or cup plate method. One thousand such units would assay about 300 to 800 units to 1 mg. of base, more nearly the latter. However, in any given case, the variability in unit strength as determined by assay of any known dilution, furnishes

proof that streptomycin is not as yet a pure product.

Enough evidence has been produced to prove its therapeutic efficacy, both in test animals and in man, in a limited number of diseases. No serious reactions have been thus far disclosed. In colon bacillus infection, Hemophilus influenza and in meningitis due to this latter organism, in the Salmonella group and the Friedländer infections,[16] it has achieved its greatest triumphs. Despite the striking results *in vitro* with the typhoid organism, clinically it has been disappointing. Both experimental and clinical results offer a justifiable degree of hope, even of expectation. Tularemia[17,18] also has been successfully treated but undulant fever is rebellious. The surgeon may find it of value in selected cases of wound infection, but it is too early to speak of this with certainty.

Method of administration is a matter of general agreement. Romansky and Dittman[19] suggested the use of beeswax and sesame oil, of proved value in penicillin, to prolong the effect of streptomycin. Not enough evidence is extant to be able to make an unqualified statement as to blood and urine levels. Only one observer has reported induration and prolonged tenderness after many injections of streptomycin had been given.[20]

SUMMARY

This is a report of a prompt response of a blood stream and genitourinary infection by colon bacilli in a man with widespread tuberculosis of long standing, which was arrested during the exhibition of streptomycin and eight months thereafter, during which restoration to working efficiency, some gain in weight and improved health were attained. Had it been possible to obtain the drug in necessary amount when needed, it is conceivable that more definite results might have followed. After the lapse of eight months, the patient received one million units of streptomycin base daily for four days and subsequently, only 250,000 units daily for twelve days more (seven million units in sixteen days) and a specimen of 100 cc. of urine, centrifuged for one hour, failed to reveal tubercle bacilli after prolonged search. The drug was then stopped by mutual agreement because of the patient's anorexia, malaise and depression, associated with a lower blood pressure than he had ever had prior to this second period of streptomycin administration.

Acknowledgments: Sincere thanks are due to Dr. Claude P. Brown and Mr. Fred Wilson and to those of their staff of the Usona Laboratory in Philadelphia, whose interest and cooperation made possible the many studies upon the patient and also to William F. Elias, PH.D. who conducted some of the work in duplicate. Dr. Elias and his coworker[5] used a cylinder plate technic similar to that used for penicillin assay, employing a strain of B. subtilis. In our work the staphylococcus (S.M. strain) was used for which we are indebted to Dr. J. M. Carlisle of the Merck Company.

REFERENCES

1. WAKSMAN, S. A. *Soil Sc.*, 8: 7, 1919.
2. HINSHAW, H. CORWIN and FELDMAN, WM. H. Streptomycin: a summary of clinical and experimental observations. *J. Pediat.*, 28: 269, 1946.
3. FELDMAN, W. H., HINSHAW, H. CORWIN and MANN, FRANK C. Streptomycin in experimental tuberculosis. *Am. Rev. Tuberc.*, 52: 269, 1945.
4. HINSHAW, H. C. and FELDMAN, W. H. Streptomycin in treatment of clinical tuberculosis: a preliminary report. *Proc. Staff Meet., Mayo Clin.*, 20: 313, 1945.
5. REIMANN, HOBART A., ELIAS, WM. F. and PRICE, ALISON H. Streptomycin in typhoid. A pharmacologic study. *J. A. M. A.*, 128: 175, 1945.
6. ZINTEL, HAROLD A., FLIPPIN, HARRISON F., NICHOL, ANNA C., WILEY, MARJORIE M. and RHOADS, J. E. Studies on streptomycin in man. Absorption, distribution, excretion and toxicity. *Am. J. M. Sc.*, 210: 421, 1945.
7. ANDERSON, DONALD G. and JEWELL, MARJORIE. The absorption, excretion and toxicity of streptomycin in man. *New England J. Med.*, 233: 485, 1945.
8. KUEHL, FREDERICK A. JR., PECK, ROBERT L., WALTI, ALPHONSE and FOLKERS, KARL. *Science*, 102: 34, 1945.
9. RAKE, GEOFFREY, HAMRE, DOROTHY, KAVANAGH, FREDERICK, KUERBER, WALTER L. and DONDROVICK, RICHARD. On the toxicity of streptomycin. *Am. J. M. Sc.*, 210: 61, 1945.
10. WAKSMAN, S. A. *Soil Sc.*, 8: 7, 1919.
11. WAKSMAN, S. A. and WOODRUFF, H. B. Soil as source

of microorganisms antagonistic to disease-producing bacteria. *J. Bact.*, 40: 581, 1940.

12. Schatz, Albert, Bugie, Elizabeth and Waxman, Selman A. Streptomycin, a substance exhibiting antibiotic activity against gram positive and gram negative bacteria. *Proc. Soc. Exper. Biol. & Med.*, 55: 66, 1944.
13. Robinson, Harry J., Smith, Dorothy G. and Graessle, Otto, C. Chemotherapeutic properties of streptomycin. *Proc. Soc. Exper. Biol. & Med.*, 57: 226, 1944.
14. Robinson, Harry J. and Smith, Dorothy G. Streptothricin as a chemotherapeutic agent. *J. Pharmacol. & Exper. Therap.*, 82: 390, 1944.
15. Heilman, Dorothy H. A method for estimating the concentration of streptomycin in body fluids. *Proc. Staff Meet., Mayo Clin.*, 20: 138, 1945.
16. Heilman, F. R. Streptomycin in the treatment of experimental injections with microorganisms of the Friedländer group, Klebsiella. *Proc. Staff Meet., Mayo Clin.*, 20: 33, 1945.
17. Heilman, F. R. Streptomycin in the treatment of experimental tularemia. *Proc. Staff Meet., Mayo Clin.*, 19: 553, 1944.
18. Foshay, L. and Pasternack, A. B. Streptomycin treatment of tularemia. *J. A. M. A.* 120: 393 1946.
19. Romansky, M. J. and Rittman, G. E. Method of prolonging action of penicillin. *Science*, 100: 196, 1944.
20. Anderson, Donald G. and Jewell, Marjorie. The absorption, excretion and toxicity of streptomycin in man. *New England J. Med.*, 233: 485, 1945.

Marked Insulin Resistance in Diabetes Mellitus*

MAXWELL G. BERRY, M.D. *and* FERDINAND C. HELWIG, M.D.
Kansas City, Missouri

INSULIN resistance is one of the striking complications encountered in the management of diabetes mellitus. No arbitrary limit to the dosage of insulin beyond which insulin resistance can be said to exist has been established. Patients in whom total pancreatectomy has been carried out can be maintained on insulin in doses varying from 26 to 40 units daily.[1] Severe diabetics frequently require more than this amount of insulin each day and are not classified as resistant to insulin. However, when an individual requires ten or even one hundred times this amount of insulin in twenty-four hours, it can be stated that in some manner he is resistant to the usual effects of the hormone.

Various conditions have been found to increase the requirements of insulin.[2] The possible causes for insulin resistance listed by Joslin and his associates[3] are acidosis, infections, destructive processes in the pancreas, disturbance of liver function, complicating disease of other endocrine glands, hemochromatosis and disturbance in the function of the skin and muscles. Levi and Friedman[4] report a case of extreme resistance to insulin in lymphatic leukemia. Daily administration of large doses of insulin to non-diabetic patients causes elevation of the glucose tolerance curve.[5] Typhoid vaccine produces resistance to insulin in depancreatized dogs.[6] Lerman[7] believes antibody development and concentration is responsible for the development of insulin resistance. Lowell[8] reports a case in which insulin resistance and allergic phenomena were present simultaneously. Thrombosis of the hepatic artery with resistance to insulin was reported by Pollack and Long.[9] Several cases requiring very large doses of insulin have been recorded. Wiener[10] reported an instance in which he gave 3,250 units of insulin in twenty-four hours. Other cases have received in twenty-four hours 2,795 units,[11] 2,100 units,[12] 1,630 units,[13] 1,297 units,[14] 1,310 units,[15] 1,205 units,[16] and 1,720 units,[17] 4,000 units a day for four successive days,[4] 2,460 units in twenty-four hours,[18] 3,620 units in twenty hours[19] and 5,780 units in twenty-four hours[20] have also been reported.

The case which we are reporting is unusual in that 5,820 units of insulin were administered in twenty-four hours (5,460 in twenty hours). We are unable to find record of a patient who received as large an amount of insulin in this period of time.

CASE REPORT

W. M. C., a sixty-six year old white banker, was admitted to St. Luke's Hospital on December 23, 1940. He had been known to have diabetes for two years and this had been controlled by diet without insulin until two months before admission when increased thirst and polyuria developed. Since December 9, 1940, he had received 25 units of regular insulin daily but the urine had persistently contained sugar. Since December 16th he had been nauseated and for three days prior to admission he had vomited everything taken by mouth.

On admission he was mentally alert, there was no air hunger, but he was obviously weak and tired. The temperature was 98.0°F., pulse 100, blood pressure 180 systolic and 90 diastolic; there was marked pyorrhea and the pharynx was moderately red. There was a slight accentuation of the second aortic heart sound, the rhythm

* From the Departments of Medicine and Pathology, St. Luke's Hospital, Kansas City, Mo.

was regular. The non-tender liver edge was palpable a finger's breadth below the costal margin. There was slight pitting edema of both ankles.

The urine contained a trace of albumin, 4 plus sugar, 1 plus acetone and the specific gravity was 1.033; the hemoglobin was 95 per cent, the red cell count 4,000,000 and the white cell count 6,600 with a normal differential count. The non-protein nitrogen was 50 mg. per 100 cc., creatinine 1.5 mg., the chlorides 400 mg., the cholesterol 150 mg. and the sugar 400 mg. Wassermann and Kline reactions were negative, the CO_2 combining power was 36 volumes per cent and the sedimentation rate was 20 mm. in one hour.

TABLE 1

Date	Blood Sugar		Urine Sugar		CO_2 Combining Power		Insulin Units
	High	Low	High	Low	High	Low	
12-23-40	570	357	+4	+4	36	..	210
12-24-40	317	190	+4	+2	48	..	390
12-25-40	238	130	...	0	..	..	270
12-26-40	259	204	+4	0	..	..	400
12-27-40	317	119	+4	0	40	..	610
12-28-40	317	120	+4	+1	36	..	750
12-29-40	219	109	+4	0	36	..	920
12-30-40	317	209	+4	+1	32	..	880
12-31-40	357	285	+4	+3	..	..	1,740
1-1-41	715	357	+4	+4	28	4	5,820
1-2-41	218	58	+1	0	52	..	200
1-3-41	197	105	+1	0	..	..	40
1-4-41	285	179	+3	0	48	..	460
1-5-41	571	285	+4	0	40	..	1,040
1-6-41	571	357	+4	+4	34	..	1,870
1-7-41	396	190	+4	0	42	..	1,250
1-8-41	179	89	+1	0	50	..	0
1-9-41	238	109	+1	0	..	..	40
1-10-41	317	238	+3	+2	42	..	240
1-11-41	420	315	+4	+3	40	..	1,610
1-12-41	317	57	+4	0	42	..	1,300
1-13-41	139	42	0	0	40	..	0
1-14-41	163	114	0	0	56	..	0
1-15-41	238	142	+3	0	56	..	110
1-16-41	...	142	...	0	..	..	0

During the first day of hospitalization the blood sugar level remained high and the urine continued to contain sugar and acetone in spite of a total of 210 units of insulin. Marked insulin resistance continued and in spite of large doses, coma developed on January 1, 1941. Table 1 shows the high and low blood sugar, urine sugar and CO_2 combining power, together with insulin given during each twenty-four-hour period. Low grade fever was present from the first day, varying between 99.6 and 101°F. with the white blood cell count ranging between 5,600 and 10,300 and polymorphonuclear cells between 56 and 89 per cent.

Slight edema of the extremities persisted in spite of an adequate urinary output during the first eight days, and then increased as the output of urine diminished until there was a 3 to 4 plus edema of the entire lower extremities. Following marked acidosis on January 1st, the liver increased only slightly in size but ascites developed. Attempts at diuresis by various drugs failed although the specific gravity of the urine remained normal and there was never more than a heavy trace of albumin.

On the morning of January 1, 1941, the patient developed marked acidosis and coma. Insulin was given in increasing doses at intervals of about one-half hour. When it became apparent that the acidosis was increasing, insulin made by three different manufacturers in various strengths was given; three doses of protamine zinc insulin were also administered and the sites of injection were changed. In addition, 2,400 units of the total were administered intravenously. Finally one dose of 500 units of U100 insulin was given subcutaneously and following this injection the acidosis and coma responded more favorably. A total of 5,820 units was given in twenty-four hours. Almost 10,000 cc. of fluid, including 300 cc. of 5 per cent sodium bicarbonate, was given during the same period. During the morning of January 1st, after onset of the marked acidosis an attack of paroxysmal auricular tachycardia with a heart rate of 180 per minute occurred and lasted for twelve hours. Following this, the rhythm remained normal.

During the afternoon of January 2, 1941, he was mentally alert and dictated several business letters. However, the course was progressively downward from this day on. Terminally, he developed pulmonary edema and bronchopneumonia. The blood sugar one hour before death on January 16, 1941, was 142 mg. per 100 cc.

At necropsy the body showed generalized edema and the skin was faintly jaundiced. The peritoneal cavity contained about 600 cc. of clear straw-colored fluid. The peritoneal surfaces were slick and shiny except in the lesser sac in which foci of fat necrosis were observed.

The liver weighed 1,500 Gm., was moderately bile-stained and showed a low grade Laennec's cirrhosis. The gallbladder was not grossly inflamed, contained thick green mucoid bile and

three small irregular calculi, the largest measuring only 7 mm. in diameter. The pancreas did not appear particularly enlarged but the surface and repeated cross sections showed widely disseminated zones of fat necrosis throughout. The portal vein was dilated and measured about 4 cm. in circumference. The lumen was filled with a firm reddish thrombus which extended into the splenic vein; the intimal lining of both veins was smooth and shiny except near the spleen where the thrombus became firmly adherent to the endothelium. The spleen weighed 200 Gm. Its capsule was slightly wrinkled and about 2.5 cm. from the lower pole a raised area of infarction 1.5 cm. in diameter was seen. On cross section several smaller infarcts were observed. Between the infarcts the pulp was soft and showed a bluish-red mottled cut surface. The venous radicles within the spleen were dilated and filled with adherent red thrombi. The right femoral vein was occluded by a red thrombus in the upper thigh area. The other viscera showed little of gross interest aside from pulmonary edema with early bronchopneumonia, moderate benign prostatic hypertrophy and a moderate degree of cerebral edema.

On microscopic examination the liver showed a moderate increase in the perilobular fibrous tissue and considerable cloudy swelling of the parenchyma. Some foci of interstitial hemorrhage were seen and minature bile thrombi in many of the canaliculi were observed. There was also evidence of degeneration and regeneration of liver cells. The pancreas, in addition to rather marked fat necrosis, showed both interstitial hemorrhage and polynuclear leukocytic infiltration. The islets presented little notable alteration. The spleen showed thrombosis of the major venous channels and early infarction. The kidneys showed many fine focal scars infiltrated with lymphocytes. There was also advanced tubular degeneration and some bile staining of the tubular albumin. The portal and splenic veins showed laminated thrombi with classical lines of Zahn. Carmine stains of the various organs showed the liver to be poor in glycogen with little or none present elsewhere.

The anatomic diagnosis was acute disseminated pancreatitis with hemorrhage and fat necrosis; phlebothrombosis of the portal, splenic and right femoral veins; multiple infarcts of the spleen; early portal cirrhosis of the liver with cloudy swelling and bile thrombosis; cholelithiasis; bile nephrosis; pulmonary edema with terminal bronchopneumonia; cerebral edema and generalized anasarca.

DISCUSSION

Delay in absorption and impotency of the insulin used were apparently not factors in the failure of this patient to respond to the usual doses of insulin. Lipocaiac was administered during the last ten days of his life without benefit.

CONCLUSION

The case of a man, sixty-six years old, who was treated for diabetic coma by administration of 5,820 units of insulin in twenty-four hours is reported with necropsy findings.

REFERENCES

1. Waugh, J. M., Dixon, C. F., Clagett, O. T., Bollman, J. L., Sprague, R. G. and Comfort, M. W. Total pancreatectomy: a symposium presenting four successful cases and a report on metabolic observations. *Proc. Staff Meet., Mayo Clin.*, 21: 25–46, 1946.
2. Pollack, H. Conditions associated with unusual requirements for insulin. *Proc. Staff Meet., Mayo Clin.*, 8: 453–456, 1933.
3. Joslin, E. P., Root, H. F., White, P. and Marble, A. Treatment of Diabetes Mellitus. Philadelphia, 1940. Lea & Febiger.
4. Levi, J. E. and Friedman, H. T. Insulin resistance in a case of diabetes mellitus and chronic lymphatic leukemia. *New England J. Med.*, 225: 975–978, 1941.
5. Appel, J. W. and Hughes, J. The effect of large doses of insulin on glucose tolerance. *Am. J. M. Sc.*, 199: 829–833, 1940.
6. Greene, J. A., David, A. and Johnston, G. Production of insulin resistance in depancreatized dogs. *Am. J. Physiol.*, 136: 595–599, 1942.
7. Lerman, J. Insulin resistance, the role of immunity in its production. *Am. J. M. Sc.*, 207: 354–360, 1944.
8. Lowell, F. C. Immunologic studies in insulin resistance, report of a case exhibiting variations in resistance and allergy to insulin. *J. Clin. Investigation*, 23: 225–231, 1944.
9. Pollack, H. and Long, E. R. Thrombosis of hepatic artery with sudden resistance to insulin in a diabetic patient. *Arch. Path.*, 13: 530–532, March 1932.
10. Wiener, H. J. Diabetic coma requiring an unprecedented amount of insulin. *Am. J. M. Sc.*, 196: 211–217, 1938.
11. Glass, W. I., Singarn, C. L. and Pollack, H. Unusually high insulin requirements in diabetes mellitus. *Arch. Int. Med.*, 70: 221–235, 1942.
12. Strouse, S. Martin, W., Martin, H. E. and

Lyster, R. W. Insulin resistance. *Tr. A. Am. Physicians*, 56: 61–66, 1941.

13. Schloss, J. J. Insulin resistance (with observations in an unusual case). *Ann. Int. Med.*, 19: 533–548, 1943.
14. Jordan, W. R. Insulin resistance, report of two cases. *J. South. Med. & Surg.*, 106: 361–363, 1944.
15. Schreier, H. Insulin resistance. *New York State J. Med.*, 43: 1341–1343, 1943.
16. Martin, W. P., Martin, H. E., Lyster, R. W. and Strouse, S. Insulin resistance, critical survey of the literature with report of a case. *J. Clin. Endocrinol.*, 1: 387–398, 1941.
17. Regan, J. F., Westra, J. J. and Wilder, R. M. Insulin resistance, report of a case. *New England J. Med.*, 223: 745–750, 1940.
18. Wayburn, E. and Beckh, W. Insulin resistance in diabetes mellitus. *J. Clin. Endocrinol.*, 2: 511–518, 1942.
19. Gorman, R. V., Harwood, R. and White, P. D. Successful treatment of severe diabetic coma complicated by chronic laryngeal obstruction. *New England J. Med.*, 234: 500–503, 1946.
20. Lozinski, E. and Frolich, L. I. Resistance to insulin. *Canad. M. A. J.*, 46: 62–65, 1942.

Phosphorus Poisoning with Recovery Accompanied by Electrocardiographic Changes

ROBERT A. NEWBURGER M.D.,* SAMUEL B. BEASER M.D.†
New York, New York *Boston, Massachusetts*
and HARRY SHWACHMAN M.D.‡
Boston, Massachusetts

WHITE phosphorus is well known as a protoplasmic poison, producing fatty degeneration and necrosis of cells. In phosphorus poisoning[1] practically all the organs are involved, with the liver, heart and kidneys showing the greatest damage. The present report is that of a patient with phosphorus poisoning showing evidence of dysfunction of the heart, liver and hemopoietic system of moderate intensity and almost complete reversibility.

CASE REPORT

The patient was a twenty-one year old Puerto Rican soldier who was admitted to the hospital on May 20, 1945, shortly after midnight. Two or three hours earlier he had ingested, with suicidal intent, about 60 Gm. of a rat paste (Paste Electrica) containing 2½ per cent white phosphorus according to the label. He had stirred the material into a glass of beer and drained the glass. As much as 1.5 Gm. of white phosphorus may have been so ingested.§ Before admission the patient had vomited twice and complained of abdominal cramps. He was moderately uncomfortable when first examined. A gastric lavage was immediately performed, first with 60 cc. of 3 per cent hydrogen peroxide and then with 300 to 500 cc. of 1 per cent copper sulfate. After the lavage 90 cc. of 50 per cent magnesium sulfate was left in the stomach as a cathartic.[2]

§ Minimum lethal dose for adults is approximately 0.1 Gm.[1]

Physical examination revealed that the general condition of the patient on admission was good. His temperature was 97°F., pulse 88 and blood pressure 120/70. His breath had a garlic-like odor. The skin presented a grayish pallor and this persisted for two or three days. The heart sounds were of good quality and intensity, the lungs were clear and the abdominal examination was noteworthy only because of slight tenderness in the epigastric region. The liver and spleen were not palpable. The reflexes were physiologic.

Although the patient was rather restless and uncommunicative during the first eighteen hours, he became subdued and responsive thereafter. He vomited once during the night and had three watery stools. The next morning the garlic-like odor of his breath was still present. He complained of some upper abdominal soreness of diminishing intensity for about one week. Nausea was present for the first few days and anorexia for a few more. At the end of the first week the patient felt well. Treatment consisted of intravenous fluids daily for the first two days (2,000 cc. of 5 per cent glucose in normal saline with 10 mg. of thiamin chloride), and daily intramuscular injections of crude liver extract (2 cc.) and of 3.2 mg. of vitamin K for the first five days. The diet was high in carbohydrate and protein and low in fat. In addition he received psychiatric attention and was subjected to a variety of laboratory tests.

Laboratory findings consisted of the following: Blood: the red blood count and hemoglobin (photoelectric colorimeter) were normal through-

* Assistant in Medicine, New York University College of Medicine; on leave of absence in the U. S. Army.
† Assistant in Medicine, Harvard Medical School; on leave of absence in the U. S. Army.
‡ Assistant in Pediatrics, Harvard Medical School; on leave of absence in the U. S. Army.

out. The white blood count (Table I) showed a transient leukopenia and neutropenia. Platelets appeared normal in number and morphology in all blood smears. All urines and repeated stools were normal. The gastric washings had a garlic-like odor but did not glow in the dark.

TABLE I

Date	White Blood Cells Per Cu. mm.	Polymorphonuclear Leukocytes			Lymphocytes, Per cent	Eosinophiles, Per cent	Basophiles, Per cent	Mononuclears, Per cent
		Segmented, Per cent	Unsegmented, Per cent	Total, Per cent				
May 20	2,450	..	..	47	50	2	1	0
May 21	6,550	8	3	11	79	3	2	5
May 23	6,000	25	18	43	43	8	1	5
May 30	6,250	..	..	44	37	15	0	4
July 25	5,750	40	13	53	32	13	1	1

Tests showed the gastric contents to be strongly positive for inorganic phosphate (none were performed for free phosphorus). The sternal bone marrow obtained by needle puncture on May 23rd showed some toxic granulation of the granulocytes. There was no reduction in granulocyte activity and there appeared to be no maturation arrest.

TABLE II

Date	Non-protein Nitrogen mg. %	Urea Nitrogen mg. %	Cephalin-Cholesterol Flocculation Test (48 hours)	Intravenous Hippuric Acid Test: Gm. Benzoic Acid in Urine in One Hour (1.77 Gm. Sodium Benzoate)	Extron-Rose Glucose Tolerance Test		
					Fasting	½ hour	1 hour
May 21	54	13					
May 22..	..	..	4+				
May 24..	20	15					
May 25..	..	..	....	....	89	103	133
June 1...	..	..	4+	0.74	100	123	149
June 16..	..	..	3+	0.67			
July 3...	..	..	4+				
July 20..	..	..	....	....	102	106	138
July 25..	32	12	3+	0.58			
Aug. 20.	..	..	4+				
Sept. 3..	..	..	....	0.43	83	123	99
Sept. 20.	..	..	....	0.73			
Sept. 24.	..	..	1+				

Results of the various repeated liver function tests, blood non-protein nitrogen, blood urea nitrogen, and Exton-Rose glucose tolerance tests are shown in Table II. Other examinations were made with essentially normal findings as follows: Serum albumin, 3.7 Gm.; serum globulin, 3.0 Gm. on May 21st; prothrombin time, 17.0 seconds; control, 16.1 seconds on May 23rd; oral glucose tolerance test, (1.75 Gm. per Kg. body weight); fasting blood sugar, 93 mg. thirty minutes, 156 mg. one hour, 142 mg. two hours, 83 mg. three hours, 88 mg. on July 26th; icterus index of 6 and 7 on May 21st and 24th, respectively; galactose tolerance test, 0.57 Gm. of reducing substance excreted in the urine in five hours after ingestion of 40 Gm. of galactose on May 27th; blood cholesterol, 184 mg. on May 28th and bromsulphthalein test, 5 mg. per Kg. body weight, 0 per cent retention after thirty minutes on June 16th and again on September 15th.

An electrocardiogram was taken on May 22nd (two days after admission) and at less than weekly intervals thereafter. The first tracing showed lowered voltage of T_1, T_2 and T_4 and isoelectric T_3. The ascending limbs of T_1 and T_2 were straightened and T_4 assumed a cove-plane shape. It took fully one month for these changes to revert to normal, as seen in the accompanying illustration.

Roentgenograms of the forearm and wrist on July 28th were normal.

COMMENTS

Various observations made on this patient are worthy of note. Leukopenia and neutropenia, although not alarming, were quite definite. Similar blood findings were present in the case reported by Chretien.[3] Because of the transient nature of the change, it is conceivable that it may have been over-

Electrocardiograms A, B and C, taken two, thirty-seven and fifty-one days, respectively, after the ingestion of white phosphorus. Note in A the lowering of the voltage of $T_{1, 2}$ and $_4$ and isoelectric T_3, also the straightening of the ascending limb of T_1 and T_2 and the cone-plane shape of T_4. Reversion toward normal is noted in the second tracing.

looked in other reported cases. The bone marrow, although obtained promptly, showed only minimal changes.*

The electrocardiographic changes, confined to moderate T wave abnormalities, are definite although not sufficiently characteristic to be considered specific. The causes of diminution in T wave voltage are many, but we are aware of only one other known case report of T wave changes attributable to phosphorus poisoning.[4] The changes in that case were very similar to those of ours. An abrupt type of exitus, possibly cardiac in origin, has been described as occurring in the first day or two in cases of phosphorus poisonings.† The cardiovascular factor, which has usually been neglected both clinically and electrocardiographically in the reported cases of phosphorus poisoning, should be considered more carefully in the future for information which may prove of value in treatment.

The evidence for significant acute liver involvement included an increased blood non-protein nitrogen level, concomitantly with a low normal blood urea nitrogen level. This abnormal ratio returned to normal in a relatively short time. Bile pigment metabolism remained intact throughout. The cephalin-cholesterol flocculation test of Hanger was abnormal when first done on May 22nd, and remained abnormal during a four-month period. The intravenous hippuric acid test for Quick became progressively abnormal until the final test on September 20th which gave a result within normal limits. This course of the liver damage stands in contrast to the rapidly reversible disturbance of the myocardium and the hemopoietic system, and is in accord with the well known hypersusceptibility of the liver to phosphorus.

SUMMARY

1. A case of ostensibly mild phosphorus poisoning is presented.

* Dr. William Dameshek was kind enough to review the bone marrow smears.

† Electrocardiographic changes of similar nature, and likewise unsuspected clinically, are described as occurring during the course of Fuadin therapy;[5] after that, two, sudden deaths have been reported.

2. Changes were found in the hemopoietic, hepatic and cardiovascular systems.

3. The significance of the T wave changes in the electrocardiogram is discussed.

REFERENCES

1. Gonzales, Thomas A., Vance, Morgan and Helpern, Milton. Legal Medicine and Toxicology. P. 492. New York, 1937. D. Appleton-Century Company, Inc.

2. Goodman, Louis and Gilman, Alfred. The Pharmacological Basis of Therapeutics. P. 615. New York, 1941. The Macmillan Company.

3. Chretien, T. E. Acute phosphorus poisoning: report of a case with recovery. *New England J. Med.*, 232: 247–249, 1945.

4. Dathe, Richard A. and Nathan, David A. Electrocardiographic changes resulting from phosphorus poisoning. *Am. Heart J.*, 31: 98–101, 1945.

5. Beaser, Samuel B. and Rodriguez-Molina, Raphael. Electrocardiographic changes occurring during treatment with fuadin. *Am. Heart J.*, 32: 634, 1946.

AUTHOR INDEX VOLUME IV

Abels, J. C., 163
Althausen, T. L., 208
Anderson, R. C., 637
Armstrong, S. Howard, Jr., 390

Baehr, George, 66
Banyai, Andrew L., 836
Barnett, Henry L., 760
Barr, David P., 331
Barton, Robert M., 447
Bauman, Eli, 710
Beard, Owen W., 228
Beaser, Samuel B., 928
Benditt, Earl P., 663
Berry, Maxwell G., 923
Blood, David W., 83
Boots, Ralph H., 702, 710
Boyle, Margaret N., 373
Bradley, Stanley E., 398
Brannon, E. S., 193
Bryner, Sergius, 671

Clark, Thomas E., 606
Clark, William H., 671
Cohen, Abraham, 911
Collen, Morris F., 383
Coss, James A., Jr., 702, 710

Dankner, Arnold, 55
Deitrick, John E., 3
Dexter, Lewis, 279
Dobson, R. Lowry, 383
Dolowitz, David A., 856
Dowling, Harry F., 716
Drew, A. Leslie, 365

Eagle, Harry, 343
Evans, James A., 806

Farnsworth, Edith B., 338
Feitelberg, Sergei, 798
Field, William W., 154
Finland, Maxwell, 473
Fleischner, Felix G., 791
Friedlaender, Alex S., 863
Friedlaender, Sidney, 863

Gastineau, Clifford F., 175
Gendel, Benjamin R., 309
Glaser, Robert J., 55
Glusman, Murray, 653
Gold, Harry, 1
Goldberger, Emanuel, 243
Goldblatt, Harry, 100
Goldring, William, 875
Goldstone, Milton E., 612
Grace, William J., 331
Greenberg, Morris, 866
Gregersen, Magnus I., 503
Groen, J., 814
Guarneri, Victor, 806
Guilford, Frederick R., 633

Hamann, Anna, 511
Hamburger, Morton, Jr., 690
Harford, Carl G., 55
Harvey, A. McGehee, 37
Haunz, Edgar A., 237
Helwig, Ferdinand C., 923
Hirsh, Harold L., 716
Hock, Charles W., 511
Holbrook, Arthur A., 525
Holmes, Joseph H., 503
Homburger, F., 163

Jolliffe, Lealie S., 473

Kabat, Elvin A., 653
Kaplan, Lawrence I., 846
Kempner, Walter, 545
Kissane, R. W., 606
Knaub, Vesta, 653
Koons, R. A., 606
Kroll, Mark M., 309
Kunkel, Henry G., 201

LaDue, Charles N., 447
Leone, Alfred D., 309
Levy, Robert L., 89
Lewis, C. S., 856
Lilienthal, J. L., Jr., 186
Lindsay, Stuart, 765
Lipman, Miriam Olmstead, 702, 710
Lloyd, Charles W., 315
Luisada, Aldo A., 791

Mason, Harold L., 175
Mathes, Sydney B., 55
Megibow, Raymond S., 798
Motley, Lyle, 539
Mufson, Isidor, 73

Newburger, Robert A., 928

O'Neill, James B., 355

Palmer, Walter Lincoln, 511
Parker, Frederic, Jr., 473
Perera, George A., 83, 416
Pomeranz, Maurice M., 612
Power, Marschelle H., 175
Priest, Walter S., 355

Quimby, Edith H., 73

Rantz, Lowell A., 671
Read, Hilton S., 846
Robertson, O. H., 690
Robertson, Wm. Egbert, 916
Robinson, Jay A., 716
Rodrigues, Jose, 511
Roth, Irving R., 493
Ruskin, Arthur, 228

Schaffer, Randolph L., 228
Scheele, Leonard A., 471
Schein, Joseph, 66
Schlesinger, Edward B., 365
Schroeder, Henry A., 578
Schwartz, Sidney P., 243
Shay, Harry, 215
Shorr, Ephraim, 3, 120
Shwachman, Harry, 928
Simons, Donald J., 760
Siplet, H., 215
Smith, Beverly C., 73
Smith, Harry L., 237
Smith, Homer W., 724
Smith, Paul K., 645, 649
Smithwick, R. H., 744
Sprague, Randall G., 175
Stead, E. A., Jr., 193

Tillett, William S., 159
Tillisch, Jan H., 629, 633
Tucker, Harold A., 343
Tumulty, Philip A., 37
Turner, Roy H., 789

Walker, Sheldon A., 663
Warren, J. V., 193
Warthin, Thomas A., 827
Weens, H. S., 193
Wégria, René, 373
Wells, Roe E., Jr., 760
Whedon, G. Donald, 3
Wigodsky, Herman S., 629
Williams, Robert H., 315
Wintrobe, Maxwell M., 313
Wood, Barbara, 365
Wood, W. Barry, Jr., 627
Woodruff, I. Ogden, 248

Young, N. F., 163

Zierler, K. L., 186

SUBJECT INDEX VOLUME IV

(E.) = Editorial

Abstracts of papers of Southern Society for Clinical Research, 452
of papers of Western Society for Clinical Research, 616
of papers of American Federation for Clinical Research, 773
Addison's disease, 11-dehydrocorticosterone in, 175
Agranulocytosis in tertian malaria, 309
Airsickness, treatment of, 649
Albumin therapy, serum, in internal medicine, 390
Alkalosis, complications of, 331
Allergy, parenteral benadryl in, 863
American Federation for Clinical Research, 773
Amyloidosis and nephrosis, 765
Aneurysm, ventricular, electrocardiographic patterns of, 243
Antibiotic age (E.), 159
Aortic valve, traumatic rupture of, 606
Arthritis, penicillin in, 710
Auricular fibrillation and heart block, 237
Aviation
medicine in, 633
physiologic problems in, 629

Bacteremia after dental extraction, 55
BAL (E.), 1
Benadryl, parenteral, in allergy, 863
Blast hypertension, 228
Book reviews
Diseases of the Nose and Throat (Imperatori), 470
Integrated Practice of Medicine (Hyman), 158
Medicine in the Changing Order (New York Academy of Medicine), 626
Principle and Practice of Medicine (Christian), 470

Cancer research (E.), 471
Cardiac
disease with vocal cord paralysis, 856
failure, 142
Cardiovascular-renal disease and hemoglobinuria, 594
Cardiovascular syphilis, 248
Cerebrospinal fluid, estimation of albumin and gamma globulin in, 653
Cirrhosis, Laennec's, of liver, 315
Clinico-pathologic conferences (Washington Univ.)
Convulsions and hepatic disease, 902
Hemoglobinuria and cardiovascular-renal disease, 594
Pulmonary disease of unknown origin, 436
Recurrent progressively severe headaches leading to coma and death, 301
Rheumatic heart disease, bacterial endocarditis and cardiac failure, 142
Columbia combined staff clinics
Congenital heart disease, 886
Hepatitis, 285
Coma and death, headaches leading to, 301
Combined staff clinics (Columbia Univ.)
Congenital heart disease, 886
Hepatitis, 285
Conferences on therapy (Cornell Univ.)
Treatment of pneumonia, 423
Uses of streptomycin, 130
Cornell conferences
Treatment of pneumonia, 423
Uses of streptomycin, 130
Coronary insufficiency, clinical aspects of, 89

11-Dehydrocorticosterone in Addison's disease, 175
Desoxycorticosterone acetate in myotonic dystrophy, 186
Diabetes
insipidus, origin of thirst in, 503
mellitus, insulin resistance in, 923
Drugs
in treatment of airsickness, 649
use of, at high altitude, 645
Dystrophy
and pain in extremities (E.), 789
myotonic, 186

Edema, electrolyte partition in, 338
Electrocardiography in ventricular aneurysm, 243
Embolism, pulmonary, diagnostic problems in, 493
Endocarditis
bacteiral, 142
and penicillin, 37
subacute, resistant to penicillin, 671
sulfonamide therapy in, 66
Endocrine changes in cirrhosis of liver, 315
Erythema multiforme exudativum and pneumonia, 473
Esophageal hernia, 612

Fluorocardiography in mitral valve lesions, 791

Glutamic acid and penicillin (E.), 627
Gout in a negro family, 911

Heart
block, complete, and auricular fibrillation, 237
in pregnancy, 447
disease, congenital, 886
rheumatic, 142
Hemoglobinuria and cardio-vascular renal disease, 594
Hepatic disease and convulsions, 902
Hepatitis, 285
Hepatorenal vasotropic factors in renal hypertension, 120
Hypertension
and urologic disease, 724
arterial, and low salt diets, 578
caused by blasts, 228

essential, physiology of, 398
human, mechanisms of, 279
origin and therapy of, 875
renal, 100
vasotropic factors in, 120
surgical treatment of, 744
Hypertensive
vascular disease, 83
and rice diet, 545
diagnosis of, 416

Immobilization, effects of, on metabolic and physiologic functions, 3
Insulin resistance in diabetes, 923
Intestines, radiation injuries of, 511
Intravenous infusions, effect of, on circulation, 193

Jaundice
liver function studies in, 215
tests in, 208

Laennec's cirrhosis of liver, 315
Lichen planus, atypical, 525
Lipiodol, absorption and metabolism, 814
Liver
disease, thymol turbidity test in, 201
function studies in jaundice, 215
tests in jaundice, 208
Laennec's cirrhosis of, 315

Malaria
tertian, agranulocytosis in, 309
therapeutic, 846
Microplethysmography in patent ductus arteriosus and coarctation of aorta, 798
Mitral valve lesions, dynamics of left auricle in, 791
Mononucleosis, infectious, 154
Myanesin, 365

Nephrosis and amyloidosis, 765
Nephrotic syndrome and tridione therapy, 760
Neuropsychiatric problems of the flyer, 637
Nitrogen mustard therapy (E.), 313

Pain and dystrophy in extremities (E.), 789
Penicillin
and bacterial endocarditis, 37
and glutamic acid (E.), 627
effect of, on bacteremia after dental extraction, 55
Penicillin G, concentrations of, after injection, 343
on flora of throat and intestinal tract, 702
in arthritis, 710
in bacterial infections, 716
Penicillin-resistant non-hemolytic streptococcal subacute bacterial endocarditis, 671
Peripheral vascular system, radioactive sodium in diseases of, 73
Pheochromocytoma, 806
Phosphorus poisoning and electrocardiographic changes, 928
Pneumonia
and erythema multiforme exudativum, 473
pneumococcic type III, 383
treatment of, 423
Pregnancy and complete heart block, 447
Pulmonary
disease of unknown origin, 436
embolism, acute, diagnostic problems in, 493

Quinidine sulfate, effect of, on heart and blood plasma, 373

Radiation injuries of intestines, 511
Reiter's syndrome, 827
Renal hypertension, 100
vasotropic factors in, 120
Rice diet in hypertensive vascular disease, 545
Rickettsialpox in New York City, 866

Salt diets, low, in arterial hypertension, 578
Seminars on hypertension
Consideration of human hypertension with respect to its renal origin and therapy, 875
Diagnosis and natural history of hypertensive vascular disease, 416
Experimental renal hypertension, 100
Low salt diets and arterial hypertension, 578
Mechanisms of human hypertension, 279
Participation of hepatorenal vasotropic factors in experimental renal hypertension, 120
Physiology of essential hypertension, 398
Surgical treatment of hypertension, 744
Treatment of hypertensive vascular disease with rice diet, 545
Serum
albumin therapy in internal medicine, 390
penicillin levels, 343
proteins in syphilis, 663
Sodium
loss induced by desoxycorticosterone acetate, 186
radioactive, in disease of peripheral vascular system, 73
Southern Society for Clinical Research, 452
Streptococci, group A hemolytic, in sneezing, coughing and talking, 690
Streptomycin, 355
in Reiter's syndrome, 827
in tuberculosis and colon infection, 916
uses of, 130
Syphilis
cardiovascular, 248
serum proteins in, 663

Throat, bacterial flora in, and penicillin, 702
Thymol turbidity test in liver disease, 201

Tridione therapy and nephrotic syndrome, 760
Tubercle bacilli, examination of gastric contents for, 836
Tuberculosis treated by streptomycin, 916

Urologic disease and hypertension, 724

Vascular disease
and hypertension, 83
hypertensive, and rice diet, 545
diagnosis of, 416
Visceral disease, and neurogenic pain, 539
Vocal cord paralysis with cardiac disease, 856

Washington Univ. clinico-pathologic conferences
Convulsions and hepatic disease, 902
Hemoglobinuria and cardiovascular-renal disease, 594
Pulmonary disease of unknown origin, 436
Recurrent progressively severe headaches leading to coma and death, 301
Rheumatic heart disease, bacterial endocarditis and cardiac failure, 142
Western Society for Clinical Research, 616

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.

Associate Professor of Medicine, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK

ADVISORY BOARD

Chairman: WALTER W. PALMER, M.D., *Bard Professor Emeritus*, Columbia University College of Physicians and Surgeons, *New York;* DAVID P. BARR, M.D., *Professor of Medicine*, Cornell University Medical College, *New York;* ARTHUR L. BLOOMFIELD, M.D., *Professor of Medicine, School of Medicine*, Stanford University, *San Francisco;* FRANCIS G. BLAKE, M.D., *Sterling Professor of Medicine*, Yale University School of Medicine, *New Haven;* EUGENE A. STEAD, JR., M.D., *Professor of Medicine, School of Medicine*, Duke University, *Durham;* JOSEPH T. WEARN, M.D., *Professor of Medicine, School of Medicine*, Western Reserve University, *Cleveland.*

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., *Boston;* HARRY GOLD, M.D., *New York;* A. MCGEHEE HARVEY, M.D., *Baltimore;* GEORGE H. HOUCK, M.D., *San Francisco;* CHESTER S. KEEFER, M.D., *Boston;* T. GRIER MILLER, M.D., *Philadelphia;* WALTER L. PALMER, M.D., *Chicago;* OSWALD H. ROBERTSON, M.D., *Chicago;* EPHRAIM SHORR, M.D., *New York;* GEORGE W. THORN, M.D., *Boston;* WILLIAM S. TILLETT, M.D., *New York;* ROY H. TURNER, M.D., *New Orleans;* RUSSELL M. WILDER, M.D., *Rochester;* M. M. WINTROBE, M.D., *Salt Lake City;* W. BARRY WOOD, M.D., *St. Louis;* JOHN B. YOUMANS, M.D., *Chicago.*

Volume IV

JANUARY TO JUNE

1948

THE YORKE PUBLISHING COMPANY, INC.

NEW YORK MCMXLVIII

COPYRIGHT, 1948
BY THE YORKE PUBLISHING COMPANY, INC.
All Rights Reserved

Printed in the United States of America

CONTENTS OF VOLUME IV

ORIGINAL ARTICLES

BAL (British Anti-Lewisite)	*Harry Gold*	1
Effects of Immobilization upon Various Metabolic and Physiologic Functions of Normal Men	*John E. Deitrick, G. Donald Whedon, Ephraim Shorr*	3
Experiences in the Management of Subacute Bacterial Endocarditis Treated with Penicillin	*Philip A. Tumulty, A. McGehee Harvey*	37
Effect of Penicillin on the Bacteremia Following Dental Extraction	*Robert J. Glasser, Arnold Dankner, Sydney B. Mathes, Carl G. Harford*	55
Sulfonamide Therapy of Subacute Bacterial Endocarditis	*Joseph Schein, George Baehr*	66
Use of Radioactive Sodium as a Guide to the Efficiency of Drugs Used in Treatment of Diseases of the Peripheral Vascular System. Preliminary Report	*Isidor Mufson, Edith H. Quimby, Beverly C. Smith*	73
Hypertensive Vascular Disease. Duration of Life in a Selected Series	*David W. Blood, George A. Perera*	83
Clinical Aspects of Coronary Insufficiency	*Robert L. Levy*	89
Experimental Renal Hypertension	*Harry Goldblatt*	100
Participation of Hepatorenal Vasotropic Factors in Experimental Renal Hypertension	*Ephraim Shorr*	120
Uses of Streptomycin		130
Rheumatic Heart Disease, Bacterial Endocarditis and Cardiac Failure		142
Infectious Mononucleosis with Severe Central Nervous System Involvement	*William W. Field*	154
The Antibiotic Age	*William S. Tillett*	159
Observations on a Normal Young Woman Given Synthetic 11-Dehydrocorticosterone Acetate	*F. Homburger, J. C. Abels, N. F. Young*	163
Effects of Synthetic 11-Dehydrocorticosterone (Compound A) in a Subject with Addison's Disease	*Randall G. Sprague, Clifford F. Gastineau, Harold L. Mason, Marschelle H. Power*	175
Sodium Loss in Man Induced by Desoxycorticosterone Acetate. Study in a Subject with Myotonic Dystrophy	*K. L. Zierler, J. L. Lilienthal, Jr.*	186
Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions	*J. V. Warren, E. S. Brannon, H. S. Weens, E. A. Stead, Jr.*	193
Value and Limitations of the Thymol Turbidity Test as an Index of Liver Disease	*Henry G. Kunkel*	201
Liver Function Tests in the Differential Diagnosis of Jaundice	*T. L. Althausen*	208

Minimal Yet Adequate Program of Liver Function Studies in the Differential Diagnosis of Jaundice	*Harry Shay* *H. Siplet*	215
"Blast Hypertension." Elevated Arterial Pressures in the Victims of the Texas City Disaster	*Arthur Ruskin* *Owen W. Beard* *Randolph L. Schaffer*	228
Coexisting Auricular Fibrillation and Complete Heart Block	*Edgar A. Haunz* *Harry L. Smith*	237
Electrocardiographic Patterns of Ventricular Aneurysm	*Emanuel Goldberger* *Sidney P. Schwartz*	243
Cardiovascular Syphilis	*I. Ogden Woodruff*	248
Mechanisms of Human Hypertension	*Lewis Dexter*	279
Hepatitis		285
Recurrent Progressively Severe Headaches Leading to Coma and Death		301
Agranulocytosis in Induced Tertian Malaria	*Maj. Benjamin R. Gendel* *Major Mark M. Kroll* *Captain Alfred D. Leone*	309
Nitrogen Mustard Therapy	*Maxwell M. Wintrobe*	313
Endocrine Changes Associated with Laennec's Cirrhosis of the Liver	*Charles W. Lloyd* *Robert H. Williams*	315
Complications of Alkalosis	*William J. Grace* *David P. Barr*	331
Electrolyte Partition in Patients with Edema of Various Origins. Sodium and Chloride	*Edith B. Farnsworth*	338
Serum Concentrations of Penicillin G in Man Following Intramuscular Injection in Aqueous Solution and in Peanut Oil-Beeswax Suspension	*Harold A. Tucker* *Harry Eagle*	343
Streptomycin. A Clinical Study of Its Use in Twenty-six Cases	*Walter S. Priest* *James B. O'Neill*	355
Clinical Studies in the Use of Myanesin	*Edward B. Schlesinger* *A. Leslie Drew* *Barbara Wood*	365
Correlation between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma	*René Wégria* *Margaret N. Boyle*	373
Clinical Evaluation of the Treatment of Pneumococcic Type III Pneumonia	*Morris F. Collen* *R. Lowry Dobson*	383
Mechanisms of Action of Serum Albumin Therapy in Internal Medicine	*S. Howard Armstrong, Jr.*	390
Physiology of Essential Hypertension	*Stanley E. Bradley*	398
Diagnosis and Natural History of Hypertensive Vascular Disease	*George A. Perera*	416
Treatment of Pneumonia		423
Pulmonary Disease of Unknown Origin		436
Complete Heart Block in a Case of Pregnancy	*Robert M. Barton* *Charles N. LaDue*	447
Southern Society for Clinical Research—Abstracts of Papers Read at the New Orleans Meeting, January, 1948		452
Cancer Research	*Leonard A. Scheele*	471

Pneumonia and Erythema Multiforme Exudativum. Report of Four Cases and Three Autopsies	*Maxwell Finland, Leslie S. Jolliffe, Frederic Parker, Jr.*	473
Differential Diagnostic Problems in Acute Pulmonary Embolization	*Irving R. Roth*	493
Origin of Thirst in Diabetes Insipidus	*Joseph H. Holmes, Magnus I. Gregersen*	503
Radiation Injuries of the Intestines	*Charles W. Hock, Jose Rodrigues, Anna Hamann, Walter Lincoln Palmer*	511
Lichen Planus, Atypical. A Report of Ten Cases	*Arthur A. Holbrook*	525
Neurogenic Pain Simulating Visceral Disease	*Lyle Motley*	539
Treatment of Hypertensive Vascular Disease with Rice Diet	*Walter Kempner*	545
Low Salt Diets and Arterial Hypertension	*Henry A. Schroeder*	578
Impulsive Behavior in a Crippled Boy		588
Hemoglobinuria and Cardiovascular-Renal Disease		594
Traumatic Rupture of the Aortic Valve	*R. W. Kissane, R. A. Koons, Thomas E. Clark*	606
Esophageal Hiatus Hernia	*Maurice M. Pomeranz, Milton E. Goldstone*	612
Western Society for Clinical Research—Abstracts of Papers Read at the San Francisco Meeting, November, 1947		616
Penicillin and Glutamic Acid	*W. Barry Wood, Jr.*	627
Physiologic Problems in Aviation	*Herman S. Wigodsky, Jan H. Tillisch*	629
Medicine in Aviation	*Jan H. Tillisch, Frederick R. Guilford*	633
Neuropsychiatric Problems of the Flyer	*R. C. Anderson*	637
Use of Drugs at High Altitude	*Paul K. Smith*	645
Treatment of Airsickness with Drugs	*Paul K. Smith*	649
Quantitative Estimation of the Albumin and Gamma Globulin in Normal and Pathologic Cerebrospinal Fluid by Immunochemical Methods	*Elvin A. Kabat, Murray Glusman, Vesta Knaub*	653
Serum Proteins in Syphilis	*Earl P. Benditt, Sheldon A. Walker*	663
Penicillin-resistant Non-hemolytic Streptococcal Subacute Bacterial Endocarditis	*William H. Clark, Sergius Bryner, Lowell A. Rantz*	671
Expulsion of Group A Hemolytic Streptococci in Droplets and Droplet Nuclei by Sneezing, Coughing and Talking	*Morton Hamburger, Jr., O. H. Robertson*	690
Changes in the Bacterial Flora of the Throat and Intestinal Tract during Prolonged Oral Administration of Penicillin	*Miriam Olmstead Lipman, James A. Coss, Jr., Ralph H. Boots*	702
Prolonged Administration of Penicillin in Arthritis	*James A. Coss, Jr., Eli Bauman, Ralph H. Boots, Miriam Olmstead Lipman*	710

Oral Penicillin in the Treatment of Various Bacterial Injections	*Jay A. Robinson, Harold L. Hirsh, Harry F. Dowling*	716
Hypertension and Urologic Disease	*Homer W. Smith*	724
Surgical Treatment of Hypertension	*R. H. Smithwick*	744
Nephrotic Syndrome Occurring during Tridione Therapy.	*Henry L. Barnett, Donald J. Simons, Roe E. Wells, Jr.*	760
Primary Systemic Amyloidosis with Nephrosis	*Stuart Lindsay*	765
American Federation for Clinical Research—Abstracts of Papers Read at the Midwestern Sectional Meeting, October, 1947		773
Abstracts of Papers Presented at the Western Sectional Meeting, November, 1947.		
Pain and Dystrophy in the Extremities	*Roy H. Turner*	789
Dynamics of the Left Auricle in Mitral Valve Lesions. Fluorocardiographic Study	*Aldo A. Luisada, Felix G. Fleischner*	791
Application of Microplethysmography to the Diagnosis of Patent Ductus Arteriosus and Coarctation of the Aorta	*Raymond S. Megibow, Sergei Feitelberg*	798
Pheochromocytoma. Report of a Case, with a New Diagnostic Test	*Victor Guarneri, James A. Evans*	806
Absorption and Metabolism of Lipiodol after Oral Administration. Method for the Study of Fat Absorption and Fat Metabolism in Man	*J. Groen*	814
Reiter's Syndrome. A Report on Four Patients Treated with Streptomycin	*Thomas A. Warthin*	827
Clinical Value of Examination of the Gastric Contents for Tubercle Bacilli	*Andrew L. Banyai*	836
Technical Aspects of Therapeutic Malaria	*Lawrence I. Kaplan, Hilton S. Read*	846
Left Vocal Cord Paralysis Associated with Cardiac Disease.	*David A. Dolowitz, C. S. Lewis*	856
Parenteral Benadryl in Allergy	*Sidney Friedlaender, Alex S. Friedlaender*	863
Rickettsialpox in New York City	*Morris Greenberg*	866
Consideration of Human Hypertension with Respect to Its Renal Origin and Therapy	*William Goldring*	875
Congenital Heart Disease		886
Convulsions and Hepatic Disease		902
Gout in a Negro Family	*Abraham Cohen*	911
Long-standing Case of Widespread Tuberculosis and Acute Colon Bacillus Infection Treated by Streptomycin	*Wm. Egbert Robertson*	916
Marked Insulin Resistance in Diabetes Mellitus	*Maxwell G. Berry, Ferdinand C. Helwig*	923
Phosphorus Poisoning with Recovery Accompanied by Electrocardiographic Changes	*Robert A. Newburger, Samuel B. Beaser, Harry Shwachman*	927

pH (3.8-4.4) for optimal resistance to vaginal infection

FLORAQUIN POWDER
— for office insufflation

FLORAQUIN TABLETS
— for patient's use

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE

Definite types of pathogens require definite pH ranges to thrive in the vagina. Therefore, therapy aimed at reestablishing a normal pH provides a truly physiologic approach to the treatment of vaginitis.

FLORAQUIN —a product of Searle Research—has an outstanding clinical history in the treatment of vaginal infection. Floraquin contains Diodoquin-Searle (5,7-diiodo-8-hydroxyquinoline), a potent trichomonacide and fungicide, and also carbohydrates, lactose and dextrose for glycogen production; it is properly acidulated with boric acid to encourage restoration of normal vaginal flora.

Floraquin and Diodoquin are the registered trademarks of G. D. Searle & Co., Chicago 80, Illinois.

Tales and Details

On a trip back to the home office last week, I ran into an awfully sad looking doctor in the club car one night.

It seems he had a beautiful case of hives — and he was itching like crazy. Couldn't sleep — couldn't sit still without scratching. Well — he had a sympathetic audience (I get hives from horses!) So I dug around in my briefcase and came up with some Cutter Dermesthetic Ointment. (Imagine — me prescribing for a doctor!)

If you think I'm going to say it cured his hives, you're wrong. This ointment isn't designed to cure anything — except the itch. That's just what it did in his case, but fast — and did it last! Instead of scratching, he propped his feet up for a two-hour bull session. Meanwhile, the bacteriostatic ingredients were taking care of any secondary infection his scratching might have started.

Only a doctor who has itched himself knows how grateful patients can be for relief like this. Dermesthetic Ointment has an over-lapping action, with benzyl alcohol for quick relief — phenol for intermediate relief — and benzocaine for prolonged relief.

The profession reports that it works fine on poison oak and ivy, insect bites, irritants in industry or rashes at home. When you stop to think how doggone many things cause so-called "pruritic conditions," you get a faint idea of how handy Dermesthetic Ointment can be. Patients like it, too, because it's greaseless, won't stain, and requires no bandaging.

If you'd like a sample, drop Cutter a line — or ask your detail man on his next call.

Your CDM

(Cutter Detail Man)

Cutter Laboratories • Berkeley 1, Calif.

Back Issues Wanted

(In good condition)

THE AMERICAN JOURNAL OF MEDICINE

will pay

$1.00 per copy for the following issues:

August 1946	March 1947
September 1946	April 1947
October 1946	June 1947
January 1947	January 1948
February 1947	February 1948

Send to

THE YORKE PUBLISHING COMPANY, Inc.

49 West 45th Street New York 19, N. Y.

Dermatophytosis treated with SOPRONOL® Improved

J. H.—Dermatophytosis of the feet—incapacitated; returned to work in two days

J. H., white male, age 29—incapacitated. Both feet acutely inflamed, with weeping, vesiculation, scaling. Skin was brawny, violaceous in color. Marked pain and pruritus.

Ninth day of treatment with powder and solution, Sopronol Improved. "Marked healing"—absence of symptoms, no evidence of continued activity of infection. Skin discoloration now a pale pink.

OINTMENT

Sodium propionate 12.3%
Propionic acid 2.7%
Sodium caprylate 10%
Zinc caprylate 5%

1 oz. tube preferable for use at night

POWDER

Calcium propionate 15%
Zinc propionate 5%
Propionic acid 0.25%
Zinc caprylate 5%

2 oz. canister for daytime dusting

LIQUID

Sodium propionate 12.3%
Propionic acid 2.7%
Sodium caprylate 10%

2 oz. bottle convenient for office treatment

Wyeth

PHILADELPHIA 3, PA.

Outstanding advantages of Acnomel's special new vehicle . . .

Acnomel's superior vehicle embodies an entirely new principle in topical acne therapy. To this vehicle—a stable, grease-free, *flesh-tinted hydrosol*—ACNOMEL owes the following important advantages:

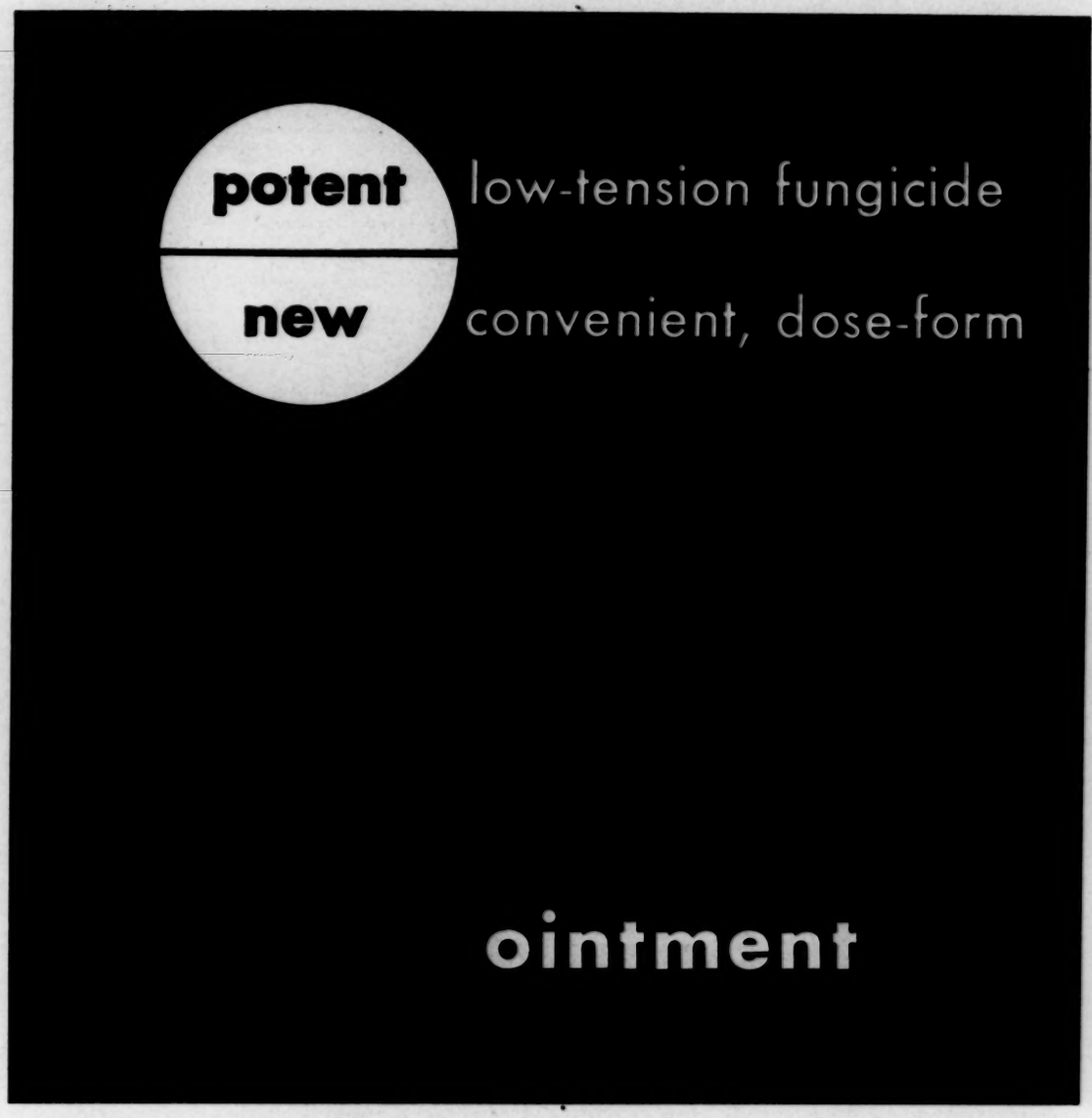
1. It is easy to apply smoothly and evenly.
2. Upon application, it dries in a few seconds.
3. Its active ingredients are maintained in intimate and prolonged contact with the affected areas.
4. It removes excess oil from the skin.
5. It is readily washed off with water.
6. It is economical, since there is no waste during application.

Smith, Kline & French Laboratories, Philadelphia

Acnomel

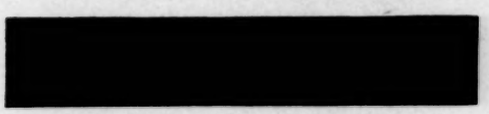
a significant advance, clinical and cosmetic,

in acne therapy



Low surface tension makes CRESATIN *metacresylacetate* one of the most penetrating and efficient of fungicides for treatment of common mycotic skin infections. It is now available in a specially compounded, clear ointment base, for maximum convenience in treatment of foot ringworm and other dermatophytoses, erythrasma, and tinea circinata, versicolor, and cruris.

CRESATIN Ointment not only exerts high fungicidal efficiency, but is analgesic, antiseptic, and mildly keratolytic as well. Finally, in contrast to its strong fungicidal action, due to volatility and low surface tension, CRESATIN Ointment is relatively and reassuringly nontoxic. Supplied in tubes containing ¼-ounce of CRESATIN *metacresylacetate*, 80%. Sharp & Dohme, Philadelphia 1, Pa.

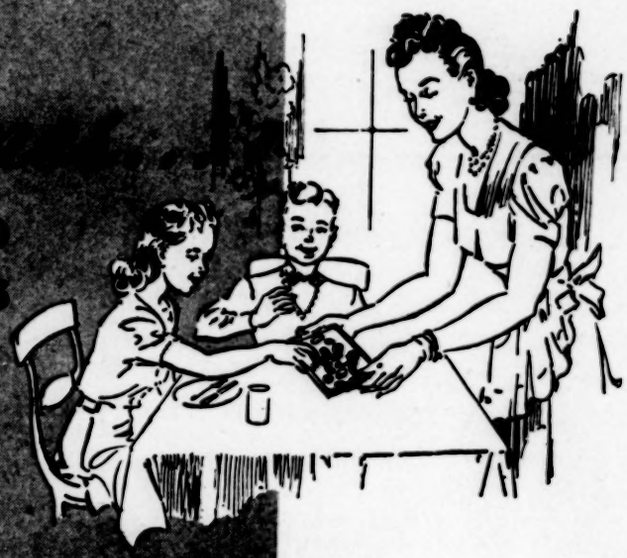


ointment

SHARP & DOHME

At times...

NOTHING IS SO SATISFYING AS A PIECE OF CANDY



Candies made with milk, butter, eggs, fruits or nuts as well as pure carbohydrates present no difficulties in digestion, have few contraindications when a general diet is allowed, and often satisfy when no other component of the dietary can.

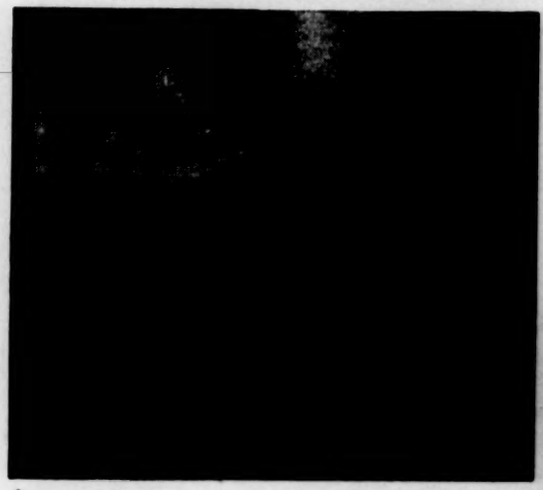
Council on Candy

NATIONAL CONFECTIONERS ASSOCIATION

1 NORTH LA SALLE ST. CHICAGO 2, ILL.

Only CHLOROPHYLL THERAPY

combines all these advantages:



Painful diabetic ulcer of about 4 months' duration which had not responded to ordinary treatment. Roentgenogram showed probable osteomyelitis. This was one of 50 cases of chronic ulcers described by Cady and Morgan in the April 1948 issue of *Am. J. of Surgery.*

- . . . accelerates healing
- . . . stimulates normal cell growth
- . . . controls superficial infection
- . . . reduces scar formation
- . . . nontoxic — bland and soothing
- . . . provides symptomatic relief
- . . . deodorizes malodorous lesions

Daily Chloresium dressings effected complete healing in 10 days. The Clinicians report: "Most (of the 50) cases constituted long, chronic, refractory problems . . . chlorophyll *(Chloresium)* therapy relieves subjective symptoms, promotes tissue growth and healing."

Reports from clinicians emphasize the effectiveness of Chlorophyll Therapy as made possible by Chloresium

BOEHME, E. J.	The Treatment of Chronic Leg Ulcers with Special Reference to Chlorophyll	The Lahey Clinic Bulletin, 4: 242, 1946
BOWERS, WARNER F.	Chlorophyll in Wound Healing and Suppurative Disease	Amer. J. Surgery, LXXIII: 37 (1947)
CADY, J. B. and MORGAN, W. S.	The Treatment of Chronic Ulcers with Chlorophyll	Am. J. Surgery LXXV: 4 (1948)
GAHAN, E., KLINE, P.R. and FINKLE, T. H.	Chlorophyll in the Treatment of Ulcers	Arch. Dermat. & Syph. 47: 849 (1943)
HOLMES, G. W. and MUELLER, H. P.	Treatment of Post-Irradiation Erythema with Chlorophyll Ointment	Am. J. Roentgenol. 50: 210 (1943)
LANGLEY, W. D. and MORGAN, W. S.	Chlorophyll in the Treatment of Dermatoses	Penn. Med. Journal Vol. 51; No. 1 (1947)
MORGAN, W. S.	Chlorophyll Therapy A Review of 114 cases	Guthrie Clinic Bulletin, 16: 94 (1947)

Chloresium

Natural, nontoxic therapeutic chlorophyll preparations.
Available at leading drugstores.

FREE! Complete literature and clinical samples of Chloresium Solution (Plain), Ointment and Nasal Solution will be sent upon request. Address. Dept. JM-5

RYSTAN COMPANY, Inc.
7 N. MacQuesten Pkwy., Mt. Vernon, N.Y.
SOLE LICENSEE — LAKELAND FOUNDATION

ESPECIALLY DURING

Post-Infectious Recovery

Following recovery from severe infectious disease, acute nutritional deficiencies must be corrected promptly if maximum speed of recovery is to be attained. The nutrient imbalance which exists during this period usually involves not only members of the vitamin B complex, but also proteins as well.

The delicious food drink made by mixing Ovaltine with milk is a pleasant and effective means of increasing the intake of virtually all essential nutrients. Easily digested and of low curd tension, it does not impose an undue digestive burden, and is frequently acceptable when other foods are refused. Three glassfuls daily supply significant amounts of B complex and other vitamins including ascorbic acid, biologically adequate protein, readily digested fat and carbohydrate, and the important minerals copper, iron, and calcium. This dietary supplement is enjoyed by all patients, young and old, and is taken without difficulty in recommended amounts. Hence it might well be included routinely in the dietary of convalescence.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B_1	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	2.00 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

***Based on average reported values for milk.**

he won't have to stay in hiding this season

. . . and many more hay fever patients will end their ostrich-like existence. They can tolerate moderate exposure to pollen, yet remain symptom-free or definitely improved—with the *new*, effective antihistaminic, THENYLENE Hydrochloride.

Written clinical reports have proved THENYLENE about 70 percent effective in hay fever cases. The incidence of side-effects is low. After receiving a number of different antihistaminics, a significant percentage of patients in one test group expressed a preference for THENYLENE Hydrochloride because of fewer side-effects.

As with all symptomatic remedies, complete relief cannot be expected in all cases; the drug should be used as an adjunct to specific desensitization wherever possible. On the other hand, THENYLENE may help patients not relieved by previous antihistaminic therapy. While no harmful effects have been reported, a total daily dose exceeding 0.4 Gm. is not recommended, nor continuous use beyond eight weeks.

THENYLENE Hydrochloride is available through prescription pharmacies everywhere in sugar coated tablets of three sizes, 25 mg., 50 mg. and 0.1 Gm. (100 mg.) in bottles of 100 and 500 tablets. ABBOTT LABORATORIES, North Chicago, Illinois.

prescribe **THENYLENE®** Hydrochloride

(Methapyrilene Hydrochloride, Abbott)

Abbott's NEW Antihistaminic

A FREE SAMPLE of THENYLENE Hydrochloride, and descriptive literature, will be sent to you on request.

Release!

from fear of conception when pregnancy is contraindicated

Physician's package and complete description of the *New Technique* will be sent upon request.

Ethically promoted—Advertised only to the medical profession.

Whenever pregnancy is contraindicated, maximal protection is assured by the new Lanteen technique. This NEW TECHNIQUE gives dual protection—the mechanical protection of the Lanteen Flat Spring Diaphragm plus the spermatocidal activity of Lanteen Jelly.

LANTEEN FLAT SPRING DIAPHRAGM

Easily fitted and long lasting. The Lanteen Flat Spring Diaphragm, collapsible in one plane only, is easily placed without the aid of an inserter. Fitting the largest comfortable size assures maximal protection.

Lanteen Diaphragms, made of the finest rubber, are guaranteed against defects for a period of one year.

LANTEEN JELLY

Lanteen Jelly, nonirritating, nontoxic, soothing and rapidly destructive to spermatozoa, combines active spermatocidal agents in a jelly readily miscible with the vaginal secretions.

Lanteen

Lanteen Medical Laboratories, Inc. • 900 North Franklin Street • Chicago 10, Illinois

Hope for [redacted] the "pelvic cripple"...

Chronic inflammation of the adnexa resulting in a fixed uterus, enlarged tortuous tubes with induration of the broad ligaments presents a therapeutic challenge to the physician.

In the treatment of chronic salpingitis and its sequelae, Jacobson's Solution produces objective evidence of improvement as well as subjective relief of pain and discomfort.

Diminution in size or disappearance of inflammatory masses has been noted even in cases refractory to other types of therapy. Both pharmacological and clinical studies have shown that its use produces increased vascularization—thereby establishing optimal conditions for the reduction of inflammation and absorption of exudate.

On this sound basis of pharmacological evidence and clinical effectiveness, Jacobson's Solution presents a therapeutic answer to an old problem—the chronically inflamed female pelvis.

Jacobson's solution

Available in 1 cc. ampules in boxes of 12 and 50.

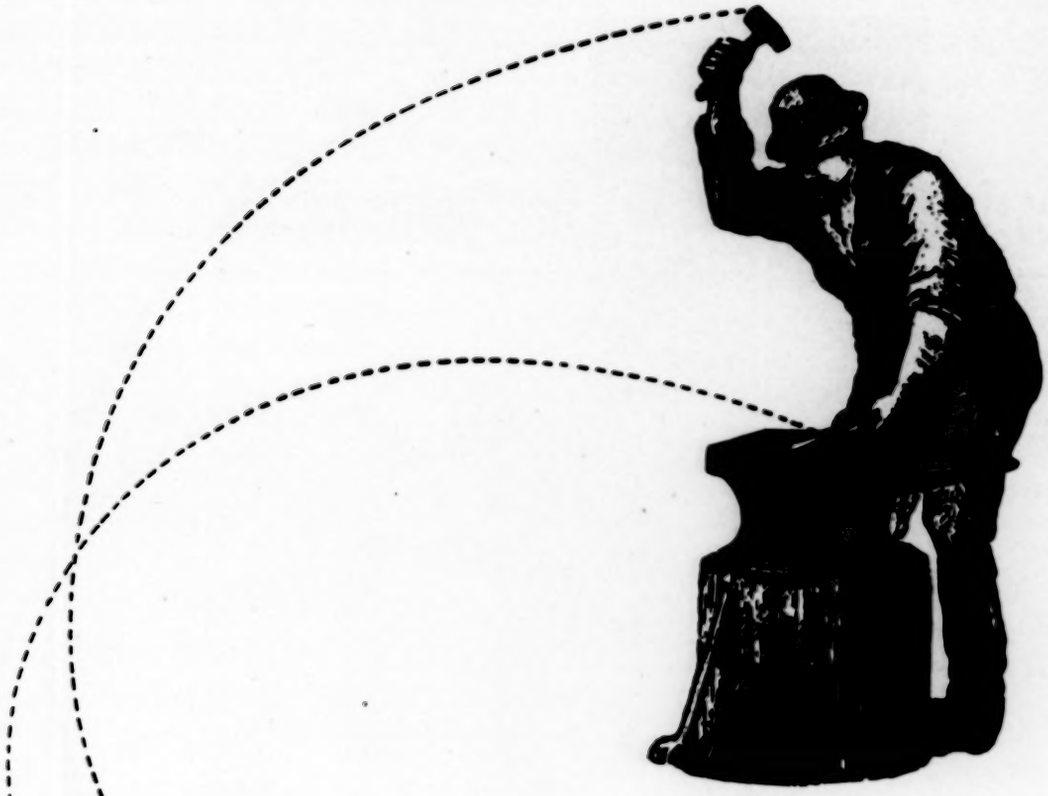
Painless upon administration and non-toxic.

HOW ADMINISTERED

Optimal results are obtained by a daily intramuscular injection of 1 cc. for 12 consecutive days. When this is not feasible, a minimum of 3 injections per week for four weeks should be given. Course may be repeated after an interval of 7 to 10 days.

For samples and literature, please address

E. Fougera & Company, Inc. • 75 Varick St • New York N Y



He too can afford a Unicap* a day ... **only 2.7c****

He too can *not* afford to be without the vitamin adequacy made simpler, more certain and more economical with a Unicap a day.

In the past 5 years **2.7c** buys less and less **food**, less shelter and less clothes

BUT 2.7c buys more and more vitamins — all these

Vitamin A	5,000 U.S.P. units
Vitamin D	500 U.S.P. units
Ascorbic Acid (C)	37.5 mg.
Thiamine Hydrochloride (B_1)	2.5 mg.
Riboflavin (B_2,G)	2.5 mg.
Pyridoxine Hydrochloride (B_6)	0.5 mg.
Calcium Pantothenate	5.0 mg.
Nicotinic Acid Amide (Nicotinamide)	20.0 mg.

Upjohn

FINE PHARMACEUTICALS SINCE 1886

in a Unicap a day

*Trademark, Reg. U. S. Pat. Off. **Available in the most economical bottle of 250 Unicaps; also in low cost units of 100 and 24